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Part II

Department of Health and Human Services

Public Health Service

National Toxicology Program; Fiscal Year 1981 Annual Plan

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicoloxy Program; Fiscal Year 1981 Annual Plan

The Director of the National Toxicology Program (NTP) announces the availability of the NTP Annual Plan for Fiscal Year 1981 and the bimonthly NTP Technical Bulletins; solicits comments on the Annual Plan and urges all interested persons to propose chemical(s) for testing by NTP.

Background

The National Toxicology Program developed scientific information about potentially toxic and hazardous chemicals which can be used for protecting the health of the American people and for the primary prevention of chemically-induced disease. The NTP centralizes and strengthens the DHHS' activities in toxicology research, testing, and test development/validation efforts and provides the necessary toxicological information needed by research and regulatory agencies. Four specific goals have been identified:

- To expand the toxicological profiles of the chemicals nominated, selected, and being tested;
- To increase the number and rate of chemicals under test;
- To develop, coordinate, and validate a series of tests/ protocols more appropriate for regulatory needs;
- To establish and use a coordinated communications network to collect, evaluate, and disseminate toxicologic information.

To accomplish these four major aims the NTP was formed by bringing together the relevant toxicological programs, people, and resources from the Public Health Service.

Presently, the four DHHS agencies whose relevant toxicology programs comprise the NTP are the National Cancer Institute, National Institutes of Health (NIH); National Institute of Environmental Health Sciences, NIH; National Center for Toxicological Research, Food and Drug Administration; and National Institute for Occupational Safety and Health, Centers for Disease Control.

The NTP Executive Committee provides linkage between DHHS research and regulatory agencies to ensure that the toxicology research, testing and test development carried out under the aegis of the NTP are responsive to the needs of those agencies and to the wants of the public. This unique and important aspect of the NTP brings together the research agencies doing fundamental biomedical research and the regulatory agencies. The governmental agencies that comprise the NTP Executive Committee are listed in the 1981 Annual Plan.

The NTP Board of Scientific Counselors provides scientific oversight of the NTP. The NTP Board advises the NTP Director and the NTP Executive Committee on scientific content, philosophy, and policy and evaluates the merit and overall quality of the science conducted in the NTP components. Eight scientists (enumerated in the 1981 Annual Plan) were appointed by the Secretary of the Department of Health and Human Services.

The program segments of the NTP are grouped into two categories—toxicological research and testing, and coordinative management activities. Individual NTP scientists have been appointed as leaders of the major program segments. Each scientist is responsible for developing (in collaboration with other NTP colleagues) the subprogram activities, the implementation plan, as well as the coordination and supervision of the program work. Program and Project Leaders are listed in the 1981 Annual Plan.

The development and approval of the NTP Annual Plan remain central to the effective planning, coordination, and operation of the National Toxicology Program. As NTP Director, Dr. David P. Rall (also the Director of the National Institute of Environmental Health Sciences) reports to the Assistant Secretary for Health.

The National Toxicology Program's third annual plan consists of two parts published separately: Part I, "NTP Annual Plan for Fiscal Year 1981" (NTP–80–62), describes current year research, testing and validation efforts, resources and past year program accomplishments. (Part I is printed in full following this announcement.) Part II, "Review of Current DHHS, DOE, and EPA Research Related to Toxicology" (NTP–81–19), lists chemicals being tested by DHHS agencies, the Department of Energy, and the Environmental Protection Agency, and describes toxicology methods currently being developed by the DHHS agencies.

Written comments on the FY 1981 Annual Plan are requested and welcome. These should be addressed to Dr. Larry Hart, Assistant to the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (telephone: (919) 541–3989 or FTS 629–3989).

Regarding chemical nomination, NTP urges all those interested in proposing chemical(s) for testing to do so, and at a minimum to give the rationale for the nomination and to recommend the type test(s) to be considered. In addition, it would be desirable (but not essential) to supplement each nomination with the following information, if known.

I. Chemical identification.
II. Production, use, occurrence, and analysis.
III. Toxicology.
IV. Disposition and structure-activity-relations.
V. Ongoing toxicological and environmental studies in the government, industry, and academia.

To bridge the yearly gap between Annual Plans, NTP started a bimonthly NTP Technical Bulletin in FY 1980 to keep those persons or groups interested in the NTP informed about the NTP's most current and proposed activities. The NTP Technical Bulletins augment the Annual Plans by more timely and frequent announcements of the NTP research activities and specific actions.

To receive the NTP Annual Plan for Fiscal Year 1981; the Review of Current DHHS, DOE, and EPA Research Related to Toxicology; or the NTP Technical Bulletin, please indicate which publications you wish to receive and submit this information to: Technical Information Section, Room A–306, Landow Building, Bethesda, MD 20205 (telephone: (301) 496–1152 or FTS 496–1152).

Dated: February 11, 1981.

David P. Rall, M.D.,

Director, National Toxicology Program.

National Toxicology Program—Annual Plan for Fiscal Year 1981

National Cancer Institute/National Institutes of Health, National Institute of Environmental Health Sciences/ National Institutes of Health, National Center for Toxicological Research/Food and Drug Administration, and National Institute for Occupational Safety and Health/Centers for Disease Control.

NTP–80–62

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NATIONAL TOXICOLOGY PROGRAM—ANNUAL PLAN FOR FISCAL YEAR 1981

Executive Summary

The National Toxicology Program (NTP) was established in November, 1978, as a Department of Health and Human Services (DHHS) cooperative effort to coordinate and manage the Department's program to develop the scientific information necessary to protect the health of the American public from exposure to hazardous chemicals.

Many human diseases can be linked with exposure to chemicals—lung cancer to asbestos, arsenic, and bis(chloromethyl)ether; liver cancer to vinyl chloride and aflatoxins; mesothelioma to asbestos; bladder cancer to benzidine; male sterility to chlordecone (Kepone), dibromochloropropane and diethylstilbestrol (DES); neurologic disease to lead, Kepone, methyl mercury and methyl butyl ketone. There are many other chemicals known or suspected to be involved in the causation of human disease. Preventing or limiting exposure to such chemicals will prevent human disease, and disease prevention is a major goal of DHHS.

NTP not only tests chemicals to determine if they are likely to cause human disease but also develops new test methods that will be more efficient and less expensive. Test method development is critical because much current test methodology is time consuming and costly, and the American public is exposed to many more chemicals than can be tested in the forseeable future by conventional methods.

Accomplishments of NTP programs during Fiscal Year (FY) 1980, and program plans for FY 1981 are described in the ensuing sections of this FY 1981 Annual Plan. Following are brief highlights of important features and accomplishments of the NTP in FY 1980:

- Increased numbers of chemicals being tested in genetic toxicology screen. There were 261 tests completed in FY 1980.
- Continued development and implementation of sequential test phases, e.g., mutagenesis testing.
- Broadened protocols in prechronic phases of the carcinogenesis bioassay to measure other toxic effects; about 70% of 40 chemical starts in FY 1980 included special studies.
- Expanded activities in the area of reproductive toxicity assessment.
- Continued validation of a comprehensive neurobehavioral test battery.
- Began interlaboratory testing of an immunotoxicology test battery.
- Began an interagency coordinated effort on benzidine-based dye mutagenesis, chemical disposition and carcinogenesis studies.
- Completed an international collaborative study of short-term testing methods for carcinogenesis.
- Changed carcinogenesis bioassay management from prime contractor to chemical manager concept.
- Initiated research to investigate modifying experimental design of the carcinogenesis bioassay to allow resultant data to be more useful for low-dose toxicology evaluation and risk assessment.
- Formed the NTP Board of Scientific Counselors and several working subcommittees of the Board.
- Formed a peer review group for reviewing and evaluating the carcinogenesis bioassay reports.
- Initiated a testing needs study.
- Published the First Annual Report on Carcinogens. The next edition planned for FY 1981 will contain information on up to 100 additional chemicals.
- Initiated a technical bulletin series as well as a literature and management tracking system.
- Completed a systems analysis examination of the research data capture needs of the NTP.
- Computerized and cross-indexed all chemicals listed as under test in the Review of DHHS Research Related to Toxicology.
- Formed an NTP Steering Committee to enhance cooperation and information exchange among participating agencies at management and laboratory levels.
- Continued activities in response to current health problems, *specifically:*

—Played an active advisory role in the Love Canal problem. Continued testing of 70 of the over 200 chemicals found in this dump site.

—Took an active role in an interagency group evaluating health effects of Agent Orange. Reproductive assessment studies in male mice have been completed.

—Continued studies on the chronic toxicology of orally administered asbestos.

The Program's accomplishments in FY 1980 and the Program's objectives in FY 1981 all relate to the NTP's aim of providing the necessary scientific information for prevention of human disease related to chemical exposure. Under this broad objective the NTP has four principal goals:

(1) to broaden the toxicological characterization of chemicals that are tested; (2) to increase the rate of

chemical testing; (3) to develop protocols appropriate for regulatory needs; and (4) to communicate Program plans and results to governmental agencies, the medical and scientific communities and the public.

Toxicological testing is divided into three major programs: cellular and genetic toxicology, carcinogenesis, and general toxicology (which includes organ-specific toxicities). The NTP's testing strategy is to identify the toxic potential of chemicals in primary screens (Phase I); confirm and further characterize toxicity (Phase II); and provide more in-depth information on chemical toxicity which can be used in scientific and public health assessments needed to determine human risk (Phase III).

The strategy for test development or validation is to evaluate existing and emerging newer methodologies to determine which may be adequately sensitive and reproducible. Those most likely to offer improvements over older methods are selected and validated. Examples of existing methodology being examined for modification are techniques used to detect heritable genetic effects, impaired kidney and pulmonary function, and neurobehavioral toxicity; new areas of methods development and validation include behavioral teratology, immunotoxicology, and short-term tests for presumptive carcinogenic potential.

The NTP's ongoing and planned efforts in toxicological testing, test development and validation as well as other key program activities such as chemical nomination and selection, information generation and dissemination, and development of an Annual Report on Carcinogens, are described in capsule form in the following pages and in more detail in the main body of the Annual plan.

Cellular and Genetic Toxicology

A continuing area of major testing emphasis is genetic toxicology. During FY 1980, 222 tests were completed in the primary screen for chemical mutagens, the *in vitro* microbial assay in *Salmonella typhimurium*. All chemicals selected for long-term bioassays are first tested using this short-term method. In FY 1981, there will be 300 chemical test starts in *Salmonella*. In addition, the *Salmonella* assay is being evaluated in an interlaboratory study aimed at determining correlation between the mutagenic response and carcinogenicity as measured by the two-year bioassay.

Two new test systems were initiated in FY 1980, a Phase I *in vitro* system using cultured mammalian cells, and a Phase II *in vivo* system using the fruit fly, *Drosophila melanogaster*. In FY 1981, there will be 50 chemical test starts in cultured mammalian cells and 60 test starts in *Drosophila*. Evaluation of potential Phase III whole animal systems, the mouse heritable translocation assay, and the mouse specific locus test, will begin.

Genetic test systems have predictive value for identification of carcinogens; however, such inferences are made on the basis of correlations. In cellular toxicology, four *in vitro* test systems which may better measure carcinogenesis (tumor formation) are being evaluated: the BALB/c 3T3 cell line, Syrian hamster embryo cell cultures, rat hepatocyte cell strains, and retrovirus-infected rat embryo cells.

Carcinogenesis Testing

The two-year carcinogenesis bioassay continues as the standard and most definitive means for detecting chemical carcinogens in animals. At the end of FY 1980, the NTP had 234 compounds in various phases of the bioassay process. Of these, 40 were new starts in prechronic testing. Twenty-four bioassays were completed and the reports were approved by an *ad hoc* review panel. The expansion of experimental protocols for about two-thirds of the bioassays started in FY 1980 was accomplished to allow better understanding of the overall toxicology of individual chemicals. In FY 1981, the NTP plans to start 45 new bioassays, all with expanded protocols, and expects to complete 34 bioassays.

General Toxicology

Acute, subchronic and chronic studies designed to characterize the toxicologic potential of several chemicals of interest to the NTP were continued or began in FY 1980. Included were studies with polybrominated biphenyls (PBBs) and chlordecone (Kepone). In test method development, the sensitivity of a number of renal function tests was evaluated; most promising were those that measured total functional capacity of the kidneys. During FY 1981, emphasis will be given to supplementing the systemic pathologic examination in 90–120-day studies.

Chemical Disposition

Information about the disposition pattern (absorption, distribution, metabolism and excretion) of chemicals is important not only for establishing correct doses of compounds for long-term bioassays, but also for understanding mechanisms of toxicity and predicting the disposition of related chemicals and chemical classes.

Current NTP capacity is 10–15 chemical disposition starts yearly. Preference is given to chemical classes, with studies on four major classes being initiated or continuing in FY 1980: aromatic and aliphatic amines, benzidine-based dyes, haloalkyl phosphates and halogenated polyaromatics. Plans for FY 1981 call for the continuation of these ongoing studies in chemical disposition, and initiation of additional studies on 12 compounds or classes of compounds.

Immunological Toxicology

During FY 1980, several chemicals were examined for immunotoxic effects using a comprehensive battery of immunology and host resistance assays. The chemicals, diethylstilbestrol, cyclophosphamide, benzo(a)pyrene, indomethacin, and 2,3,7,8-tetrachlorodibenzo-p-dioxin, were immunosuppressive, affecting cell-mediated immunity and T-cell function, antibody PFC formation and host resistance parameters. Major areas of continuing test development include bone marrow progenitor and host resistance assays.

Neurobehavioral Toxicology

The standardization and validation of a comprehensive test battery for assessment of potential neurotoxins were continued. The tests measure sensory and motor function and indicators of learning ability. An in-depth study was conducted on neurobehavioral toxicity of chlordecone (Kepone) in adult and neonatal animals.

In FY 1981, efforts will continue to develop and standardize automated procedures to assess toxicity using basic behaviors such as eating, drinking and motor activity. Another continuing program focuses on human and animal laboratory testing and work site studies of selected chemical agents.

Pulmonary Toxicology

Major emphais was given to initiating a series of studies focused on a comprehensive evaluation of the benefits of utilizing respiratory function techniques as opposed to standard pathologic evaluation in toxicity assessment of compounds. Respiratory function was evaluated in rats after inhalation exposure to two chemicals, ozone and acrolein.

Reproductive and Developmental Toxicology

During FY 1980, tests for teratogenic potential were completed and reports received on 21 chemicals including six by the inhalation route. In FY 1981, NTP will initiate new test starts on 10–15

chemicals using conventional techniques. Some tests will use expanded protocols including single or multi-generational studies and functional testing. Male fertility was studied after treatment of mice with components of herbicide "Agent Orange." No significant decrement in fertility or reproductive capacity was noted, and there was no evidence of germ cell toxicity. Survival of offspring and neonatal development were apparently unaffected by paternal exposure to these chemicals. The pilot segment of an interlaboratory study on behavioral teratology will begin in FY 1981.

Program Resources and Planning Assumptions

The President's budget for FY 1981 ($70.1 million) permits continuation of the NTP at a slightly higher level of of funds than was obligated in FY 1980. There will be 45 new chemical starts in two-year carcinogenesis bioassays, a 17 percent increase in mutagenesis test starts, and a level effort in teratology testing. Continuing and, in some cases, expanded priorities will be given to fertility and reproductive studies, neurobehavioral toxicology, chemical disposition studies, development of short-term tests for carcinogenicity, and improvement of automated data base systems.

Program Oversight

During FY 1980, a Board of Scientific Counselors was established to provide scientific oversight of the NTP. Three Board subcommittees were formed to advise and work with Program staff in the areas of chemical nomination and selection, peer review of carcinogenesis bioassay reports, and automated data processing requirements for the bioassay programs.

Chemical Nomination and Chemical Selection

The chemical nomination and chemical selection processes set priorities for testing by NTP with regard to which chemicals to test and for which toxicologic effects to test. During FY 1980, considerable effort was made to broaden the base of people and organizations from which chemical nominations are received. Executive summaries for 127 nominated chemicals were prepared and submitted to the Executive Committee for action. In FY 1981, there will be increased efforts in preparing more detailed nominations for mutagenicity testing.

Information Generation and Dissemination

The Annual Plan and the NTP Technical Bulletin are the main communications media to keep interested persons and groups informed about the NTP's most current and proposed activities. Nearly 5,000 copies of the FY 1980 Annual Plan were distributed. The Technical Bulletin was established in FY 1980 to disseminate information about NTP test results and program activities on a more frequent basis. Two issues of the NTP Technical Bulletin were published and mailed to 3,000 individuals and organizations.

Annual Report on Carcinogens

The First Annual Report on Carcinogens, published FY 1980, focuses on 26 chemicals and industrial processes which the International Agency for Research on Cancer (IARC) has examined with respect to their potential for cancer induction in humans. The Report summarizes available human exposure data, evidence for carcinogenicity from human and animal studies, production and use data, and applicable Federal regulations. The Second Annual Report, scheduled for publication in FY 1981, will include similar information on up to 100 carcinogens.

Introduction

In November 1978, the Secretary of the Department of Health, Education, and Welfare (now the Department of Health and Human Services) (DHHS) announced the establishment of the National Toxicology Program (NTP) as a Department-wide effort to provide needed information about potentially toxic and hazardous chemicals to regulatory and research agencies, and to strengthen the science base in toxicology.

Because many human diseases are known or suspected to be caused by exposure to chemicals, preventing or decreasing human exposure to such chemicals will prevent human disease. NTP aims to develop the scientific information needed to protect the health of the American public from damage by exposure to environmental chemicals.

The Public Health Service of DHHS is responsible for safeguarding the public's health, and the prevention of human exposure to toxic chemicals remains a keystone in the Department's efforts to prevent disease and promote health.

The National Toxicology Program begins its third year in Fiscal Year (FY) 1981. The Annual Plan for FY 1981 consists of two parts (separately published):

- Research, resources, and program plans for FY 1981, and a report of program progress and accomplishments for FY 1980; and
- Review of current DHHS research related to toxicology.

For the first time the Annual Plan separates annual report information (FY 1980) from planned activities (FY 1981). Summary information for work completed during FY 1980 is given for each toxicologic research and testing activity, and coordinative management function. Also for the first time, the second part of the Annual Plan includes a review of research related to toxicology by the Environmental Protection Agency (EPA) and the Department of Energy (DOE).

Nature of the Problem

Chemical contamination of the human environment has been steadily increasing for the last 150 years or more; and since World War II, man-made pollution has multiplied. These phases coincide with the Industrial Revolution, and with the creation of a complex chemical industry which continues to introduce an estimated 700 to 1000 *new* chemicals into commerce each year.

Tragic incidents such as the exposure of workers at Hopewell, Virginia, to Kepone (chlordecone) and the exposure of humans and livestock in Michigan to polybrominated biphenyls (PBBs) dramatically emphasize the potential for harm posed by chemical pollutants. International episodes include the reaction vessel explosion (dioxins) in Seveso, Italy, and the Yusho contamination (PCBs) in Japan. In a broader perspective, the first report of the Federal Task Force on Environmental Cancer and Heart and Lung Disease, presented to Congress on the first anniversary of the Clean Air Act, stated that cancer, heart and lung disease account for about 60% of all deaths each year. Growing evidence links much of the occurrence of these diseases to sources in the environment.

More recently, the issue of large numbers of chemical waste dumps existing around the country has added urgency to the need for scientific information which identifies and characterizes chemicals in the environment which are potentially toxic to humans. Chemicals so far identified in such dumps are known to cause both acute and chronic illnesses. Although the scope of the health problems that may derive from chemical waste dumps cannot be precisely defined at present, the EPA estimates that as many as 30,000 waste dump sites may pose significant health problems. To the backlog of existing potential chemical

hazards must be added new ones, such as those that may result from new ways of producing energy. Some of the byproducts from coal liquefaction-coal gasification, for instance, have been shown to cause toxicity in general and carcinogenesis in particular.

Nearly 60,000 chemicals are used in commerce in the United States, and humans are exposed in varying degrees to most of them. Fortunately, not all of these chemicals are hazardous to humans. Thus, to protect the public health and to prevent disease, the fraction posing health threats to humans must be accurately identified and controlled.

This then is the major task of the National Toxicology Program—to identify those chemicals considered toxic to humans and that must be controlled to prevent disease.

Testing Needs Study

The limited trained manpower, laboratory facilities and financial resources available allow only a small number of chemicals to be characterized as to their toxicology potential relative to the national need to test chemicals of potential public health concern. To provide the NTP with decision-making guidelines by which to orient its testing activities, the National Academy of Sciences (NAS) starting in early FY 1981 has undertaken an extensive Testing Needs Study. This study will define the universe of chemicals in existence and make judgments as to what proportion of the universe has potential public health implications. Some of the criteria to be used include the potential for human exposure, known toxicity of a given chemical and adequacy or inadequacy of the data base. Those chemicals specifically identified will be sent to the NTP and its Executive Committee for their consideration, along with agency inputs, public inputs, etc. The NAS will develop a system, for NTP consideration, to assist NTP in their undertaking a setting of priorities among all chemicals submitted for NTP consideration for testing.

Objectives of the National Toxicology Program

Within the framework of its charge to identify those chemicals potentially toxic to humans, the broad goal of the NTP is to coordinate and strengthen the activities of the Department of Health and Human Services in testing chemicals of public health concern, as well as to develop and validate new and better integrated test methods. Four specific goals have been identified:

—To expand the toxicologic profiles of the chemicals nominated, selected, and being tested. In the carcinogenesis bioassay process, a variety of special studies were integrated into prechronic and chronic experiments during FY 1980.

—To increase the rate of chemical testing. The rate of chemical testing for carcinogenesis increased markedly during the first year of the Program and the rate of testing for mutagenic effects has increased each year.

—To develop, coordinate, and continue to validate a series of tests and protocols more appropriate for regulatory needs. The protocol for the two-year carcinogenesis bioassay has been broadened to include special studies aimed at detecting other types of toxicity during the acute and 90-day testing phases. Test batteries for the assessment of genetic, neurobehavioral, and immunological toxicology have been or are being developed and validated.

—To establish a coordinated communications network to collect, evaluate, and disseminate toxicologic information concerning data compilation, test results, method development and validation, and other Program activities. As a complement to the Annual Plan, a NTP Technical Bulletin began publication in FY 1980.

Significant progress toward these objectives has been achieved during the first two years of the NTP.

Future Aims and Needs

During the first two years of its existence, the NTP has made significant progress towards its objectives. Yet, much remains to be accomplished. Some of the Program's aims and needs can be highlighted:

- To involve agencies, other than the participating agencies, more actively in NTP planning and activities concerned with toxicology research, chemical testing, and method development and validation.
- To extend the annual Review of Federal Agency Support for Toxicology Related Research to other Federal agencies involved in toxicology activities. Information from the Environmental Protection Agency (EPA) and the Department of Energy is included in the FY 1981 Review.
- To obtain more input from the scientific community into NTP research and testing activities. The FY 1981 NTP Open Meeting will be held concurrently with a major toxicology society annual meeting.
- To better define gap areas in environmental toxicology and develop research and testing activities in such areas.
- To increase and speed up public dissemination of research, testing, and method development and validation results, e.g., it is planned to publish separate technical reports on results of studies from the prechronic phases of the carcinogenesis bioassay process.
- To continue joint briefings on chemicals and chemical classes of public health concern, bringing scientists doing the research together with scientists and program officials from regulatory agencies which are in need of specific data to support regulations, e.g., on benzidine-based dyes, phthalates (proposed).
- To improve NTP management tracking systems.
- To develop and evaluate methodology for testing mixtures and combinations of chemicals. This will require extensive input and cooperation from scientists and scientific groups in various agencies and non-governmental organizations.

Participating Agencies

Resources for the National Toxicology Program in FY 1980 came from the budgets of these participating DHHS agencies:

National Cancer Institute/National Institutes fo Health (NCI/NIH),
National Institute of Environmental Health Sciences/National Institutes of Health (NIEHS/NIH),
National Center for Toxicological Research/Food and Drug Administration (NCTR/FDA), and the
National Institute for Occupational Safety and Health/Centers for Disease Control (NIOSH/CDC).

The Director of the NTP is Dr. David P. Rall, also the Director of the National Institute of Environmental Health Sciences. For the purpose of this program, he reports to the Assistant Secretary for Health, DHHS.

Each year, when resources of the participating agencies are identified, memoranda of understanding are prepared and signed by the head of each agency and the NTP Director. These memoranda:

1. Specify those resources to be devoted to the Program.
2. Identify Program components by organizational title.
3. Identify supporting elements of the agencies, and their responsibilities.

The capabilities of the NTP are also augmented through an interagency agreement with the National Library of Medicine that provides the NTP with toxicology-related portions of its technical information services.

Three other agencies (the Occupational Safety and Health Administration, the Consumer Product Safety Commission, and the

Environmental Protection Agency) are represented on the NTP Executive Committee, thus assuring their input into the Program. Other Governmental agencies with a health-oriented mission are invited to become participating members of the NTP and contribute toxicology-related resources to the Program.

Resources and Planning Assumptions

The NTP's FY 1980 obligations were $66.7 million. This funding, as well as staffing, represents an allocation of resources from the four contributing agencies. The President's budget for FY 1981 permits the continuation of NTP at a slightly higher level, $70.1 million, than the FY 1980 level. Because Congressional action on the FY 1981 budget was not yet complete at the time of this report, the NTP Annual Plan for FY 1981 is based on a level of $70.1 million. The President's budget for FY 1981, compared with the actual obligations for FY 1979 and FY 1980, is shown in Figure 1.

Assuming the final appropriated budget is similar to the President's budget, the following planning assumptions can be made:

(1) There will be 45 new chemical starts for two-year carcinogenesis bioassays.

(2) Mutagenesis testing starts will increase by about 17% due primarily to increased efficiency in new Phase I and Phase II assays.

(3) The teratology testing effort will remain level.

In addition, priority will be given to modest increases of effort in the areas of fertility and reproduction, neurobehavioral toxicology, chemical disposition, and development of short-term tests for carcinogenicity.

In sum, the NTP activities for FY 1981 represent a reasonably balanced approach to fulfilling the specific goals established for the NTP and endorsed by the Executive Committee.

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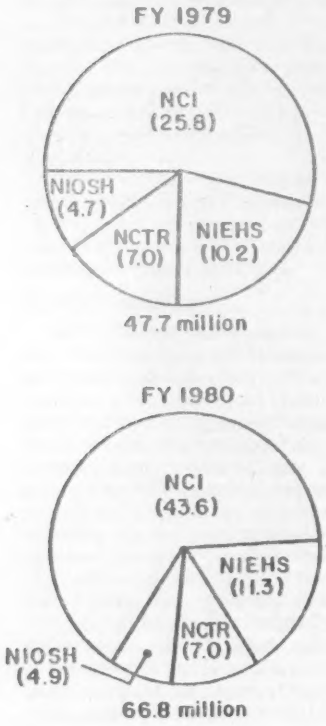
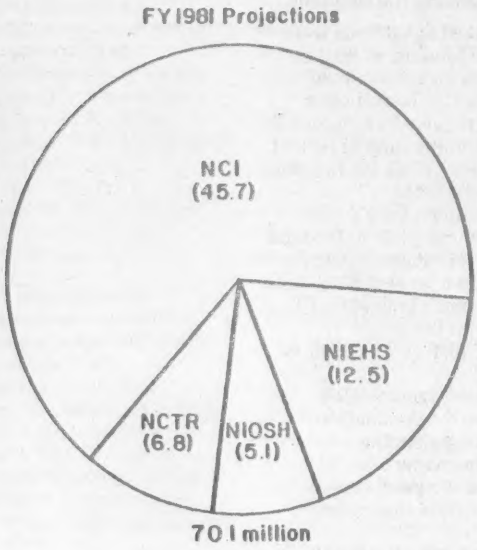
FIGURE 1

AGENCY ORIGIN AND AMOUNTS OF FUNDING
(millions)

Historical Data(actual)





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Oversight and Review

NTP Executive Committee

Primary oversight for the National Toxicology Program is provided by the NTP Executive Committee. Members of the committee are:

Dr. Eula Bringham, Assistant Secretary of Labor for Occupational Safety and Health Administration, Department of Labor (Chairperson)
Mr. Douglas Costle, Administrator, Environmental Protection Agency
Dr. Vincent T. DeVita, Director, National Cancer Institute
Dr. Donald S. Fredrickson, Director, National Institutes of Health
Dr. Jere Goyan, Commissioner, Food and Drug Administration
Ms. Susan B. King, Chairman, Consumer Product Safety Commission
Dr. David P. Rall, Director, National Institute of Environmental Health Sciences
Dr. Anthony Robbins, Director, National Institute for Occupational Safety and Health

The Chairperson is elected by the Committee and serves a one-year term. Active participation of Committee members at regular meetings assures continuing involvement of the research and regualtory agencies in the critical phases of operation: development and approval of chemical selection principles; a chemical nomination and selection process; protocol design and approval policy; selection and priority setting for chemicals to be placed on test; and input into program planning and balance. Committee members will continue their oversight in FY 1981 by actively monitoring and evaluating the progress of the Program and advising on future research and testing needs. This unique and important aspect of NTP continues to bring together agencies performing fundamental biomedical research and the regulatory agencies who need these results.

NTP Board of Scientific Counselors

The National Toxicology Program Board of Scientific Counselors provides scientific oversight of the NTP. The Board advises the Director and the Executive Committee on scientific content, philosophy, and policy matters and evaluates the merit and overall quality of the science conducted in the Program's components.

The Charter of the Board of Scientific Counselors was adopted by the Executive Committee and the following eight scientists were appointed in FY 1980 by the Secretary, DHHS:

- Norton Nelson, Ph.D. (Chairperson), Professor of Environmental Medicine, New York University School of Medicine
- Joseph C. Dunbar, Ph. D., Associate Professor of Physiology, Wayne State University School of Medicine
- Curtis Harper, Ph. D., Associate Professor of Pharmacology, University of North Carolina School of Medicine
- Margaret Hitchcock, Ph. D., Assistant Professor of Pharmacology, Yale University Medical School
- Marjorie G. Horning, Ph. D., Professor of Chemistry, Baylor College of Medicine
- Mortimer L. Mendelsohn, M.D., Ph. D., Director, Biomedical Sciencies Division, Lawrence Livermore Laboratory, University of California
- Thomas H. Shepard, M.D., Professor of Pediatrics and Head of Central Laboratory for Human Embryology, University of Washington School of Medicine
- Alice S. Whittemore, Ph. D., Adjunct Professor of Family, Community, and Preventive Medicine, Stanford University.

The Board of Scientific Counselors held three open meetings during FY 1980. These meetings are summarized as follows:

January 14–15, 1980 Meeting

At the first meeting of the NTP Board of Scientific Counselors, the Program Director and participating agency representatives presented a synopsis of the NTP programs, goals and plans; described the relevant programs of the four NTP components (NCI, NIEHS, NCTR, NIOSH); and defined the role of the Board. Three areas were defined on which the Board should concentrate: (1) quality of the science and scientists in the NTP; (2) quality of the program design; and (3) chemical nomination and selection process. Topics covered in this meeting were: (1) science review; (2) chemical nomination and selection process; (3) protocol and experimental design; (4) preparation, review and dissemination of information and reports; and (5) automated data processing. Three working subcommittees were appointed from the Board membership: (1) Chemical Nomination and Selection; (2) Reports Review; and (3) Automated Data Processing. There was also a review of the first three phases of the chronic carcinogenesis bioassay process; specifically, the pretesting phase, prechronic testing, and the two-year bioassay.

April 7–8, 1980, Meeting

During this meeting, a report of the first meeting of the Chemical Nomination and Selection Subcommittee was presented during which improvements in the nomination and selection process were considered, including the need to reach a wider audience for solicitation of nominations. The final four phases of the chronic carcinogenesis bioassay process were discussed and reviewed. These are: (1) histopathologic analysis and report; (2) internal program review and analysis of data; (3) external peer review; and (4) report issuance phase. Members of the carcinogenesis testing program staff discussed the bioassay analysis and reporting activities. A Technical Reports Review Subcommittee was formed specifically to conduct peer review on technical reports from the carcinogenesis bioassay process now that the NCI Clearinghouse on Environmental Carcinogens has disbanded.

June 27–28, 1980, Meeting

The Technical Reports Review Subcommittee augmented by an *ad hoc* Panel of Experts completed peer review on nine carcinogenesis bioassay reports. The Subcommittee recommended that NTP staff focus on: (1) evaluation of methodology for statistical analysis of bioassays; (2) review of pathology quality assurance in bioassays; (3) development of guidelines concerning types of human risk statements to be used. Establishment of a mechanism for external peer review of NTP technical reports was discussed. A decision was made to continue technical report peer review using the Technical Reports Review Subcommittee and Panel of Experts. The Automated Data Processing and Chemical Nomination and Selection Subcommittees presented status reports.

Operations Management System

The Secretary, DHHS, established a management tracking system in FY 1980 for the purpose of holding DHHS agency and program heads, and senior managers, accountable for specific, major operational achievements. Called the Operations Management System (OMS), it monitors progress and effectiveness of selected program initiatives by measuring actual monthly and quarterly achievements against projected goals. The National Toxicology Program was chosen for inclusion in the OMS. The carcinogenesis bioassay and mutagenesis testing programs of the NTP, as well as the development of the

Annual Report on Carcinogens, are being monitored in FY 1980 and FY 1981.

Coordination and Communication

Central to the effective planning, coordination, and operation of the NTP is the development and approval of the Annual Plan to which all participants (NIEHS, NCI, NCTR and NIOSH) contribute. The Annual Plan consists of two parts. Part I describes the research, resources, and program activities for the past fiscal year and program plans by NTP for the current fiscal year. To measure progress toward the objectives presented in prior Annual Plans, separate annual report sections are being published concurrently for the first time in FY 1981. Part II presents a review of current research related to toxicology being conducted by various Federal agencies both inside and outside of NTP. In FY 1980 this review covered only DHHS agencies, while EPA and the Department of Energy have contributed data for the FY 1981 review.

To ensure that the efforts of the NTP remain relevant to society, NTP actively solicits and encourages comments from everyone—scientists, public and private organizations, and individuals. Partly, this is accomplished by wide distribution of the Annual Plan (published in the **Federal Register**). Open meetings are held expressly to receive comments on current and future Annual Plans and to encourage nominations of chemicals for testing. A NTP Technical Bulletin was initiated in FY 1980 to serve as the Program's major vehicle for communication to those interested in NTP's current and future activities. It is published several times a year. Recently, a NTP Public Information Office was established and will be responsible for improving communication with the national media and the public.

Federal agencies that do not participate in the NTP also have responsibilities for toxicologic research, testing, and communication of their findings. To increase interactions and exchange of information with such agencies, a briefing was held June 3, 1980, for representatives from these other Federal agencies.

The NTP is also developing liaison with foreign agency counterparts. Contacts have been established with the World Health Organization's International Program on Chemical Safety, with the International Agency for Research on Cancer, with the International Registry of Potentially Toxic Chemicals, and others.

NTP staff participate in a number of interagency liaison groups, including the DHHS Committee to Coordinate Environmental and Related Programs, the Task Force on Environmental Cancer and Heart and Lung Disease, and the Interagency Collaborative Group on Carcinogenesis.

To increase coordination and information exchange and promote interagency working relationships within the Program, the NTP has established a Steering Committee composed of the operating heads and other key staff from the participating agencies. This group meets monthly or bimonthly.

Organization

The scientific capabilities and resources of the participating agencies cover a spectrum of toxicologic techniques, methods, and disciplines. All four agencies, for instance, conduct long-term toxicity-carcinogenicity studies and some mutagenicity testing or test development. Three agencies are involved in neurobehavioral testing; two agencies study pulmonary toxicity. Individual NTP scientists have been identified as leaders of major program segments. Each individual serves as the focus or contact person for a particular program activity and is responsible for developing, in collaboration with appropriate NTP colleagues, the sub-program objectives, the plan for implementing the sub-program, as well as the coordination and supervision of the sub-program's work.

The program segments of the National Toxicology Program are grouped into two categories—toxicologic research and testing, and coordinative management activities. The toxicologic research and testing activities include all aspects of research, test method development, and testing of chemicals, ranging from the design of experiments to evaluation of the data and writing the reports or manuscripts. The coordinative management activities are overarching and serve primarily to facilitate and/or support research and testing activities, as well as to provide information on program plans and progress. The development and supervision of contracts would be management activities. The program segments and program leaders are listed in Table 1. To allow estimates of the levels of activity within particular NTP disciplinary components, the funding levels in FY 1980 allocated to each of the program areas within both toxicologic research and testing, and coordinative management activities are diagrammed in Figure 2.

During FY 1980, administrative responsibilities for the activities of the NCI carcinogenesis bioassay program were transferred to NIEHS. This action enhances the overall coordination and the management aspects of the NIH component of the NTP.

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TABLE 1

Major National Toxicology Program Areas and Leaders

Area	Leader	Contributing Agency*	Telephone Number
Director	Dr. D.P. Rall	NTP	(919) 541-3201
Deputy Director	Dr. J.A. Moore	NTP	(919) 541-3267
Toxicologic Research and Testing			
Cellular and Genetic Toxicology	Dr. R. Tennant	NIEHS	(919) 541-4130
Carcinogenesis	Dr. W. Caspary	NCI	(301) 496-1071
Cellular Transformation	Dr. R. Tennant	NIEHS	(919) 541-4141
Mutagenesis	Dr. E. Zeiger	NIEHS	(919) 541-4482
Pathology	Dr. E. McConnell	NIEHS	(919) 541-3231
Experimental Pathology	Vacant		
Toxicological Pathology	Dr. E. McConnell	NIEHS	(919) 541-3231
Tumor Pathology	Dr. J. Ward	NCI	(301) 496-6868
Pulmonary Toxicology	Dr. T. Lewis	NIOSH	(513) 684-8392
Reproductive Assessment and Developmental Toxicology	Dr. C. Kimmel**	NCTR	(501) 542-4516
Systemic Toxicology	Dr. J. Moore	NTP	(919) 541-3267
Chemical Disposition	Dr. H. Matthews	NIEHS	(919) 541-3369
Immunological Toxicology	Dr. J. Dean	NIEHS	(919) 541-4659
Neurobehavioral Toxicology	Dr. C. Mitchell	NIEHS	(919) 541-3220
Toxicological and Carcinogenesis Evaluation	Dr. J. Moore**	NIEHS	(919) 541-3267
Senior Chemical Managers	Dr. M. Dieter	NCI	(919) 541-3368
	Dr. R. Chhabra	NIEHS	(919) 541-3386

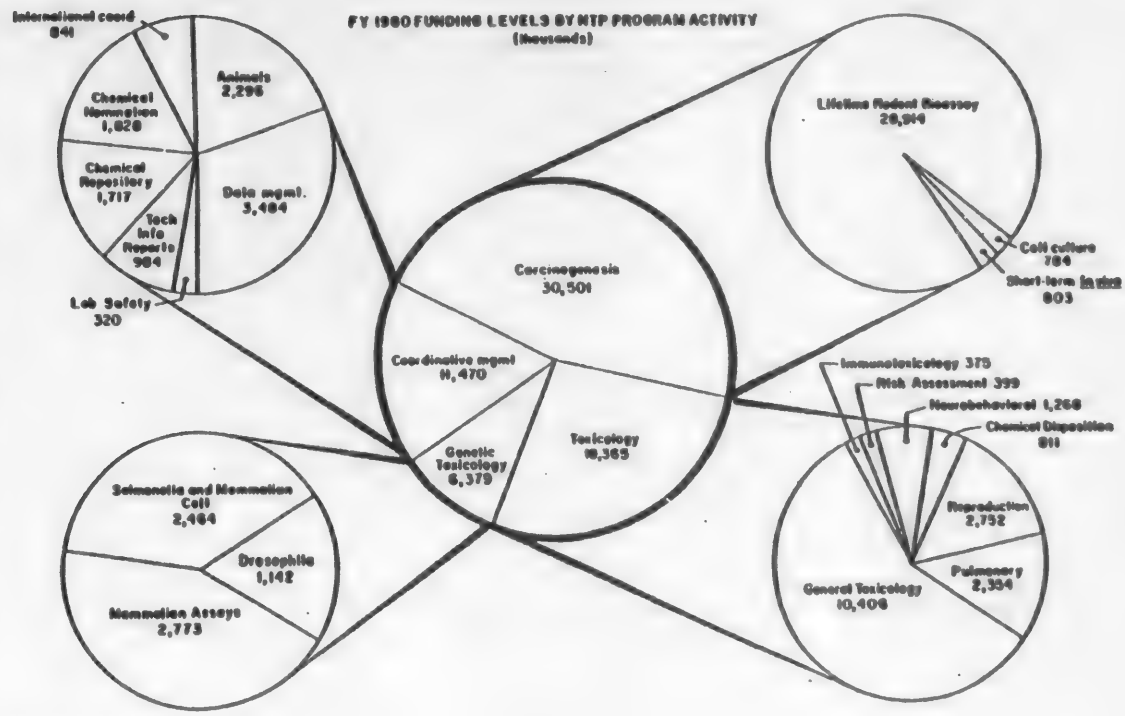
TABLE 1 (Cont'd)

Area	Leader	Contributing Agency*	Telephone Number
Coordinative Management Activities			
Chemical Nomination	Dr. L. Fishbein	NCTR	(501) 542-4390
Data Management and Analysis	Dr. D. Hoel	NIEHS	(919) 541-3441
Biostatistics	Dr. J. Haseman	NIEHS	(919) 541-3437
Data Systems	Mr. J. Washington	NIEHS	(919) 541-4497
Development	Mr. A. Konvicka	NCTR	(501) 542-4534
Information Systems	Dr. H. Kissman	NLM	(301) 496-3147
Program Operations (Bioassay)	Dr. J. Douglas	NCI	(301) 496-5591
Test Management	Dr. W. Hartwell	NCI	(301) 496-4874
Collaborative Services	Dr. C. Whitmire	NCI	(301) 496-4874
Program Resources	Dr. C. Grieshaber	NCI	(301) 496-5591
Animal Resources	Dr. G. Boorman**	NIEHS	(919) 541-3231
Chemistry (Repository)	Dr. C. Jameson	NCI	(919) 541-3355
	Dr. D. Walters	NIEHS	(919) 541-3355
Health and Safety	Dr. D. Walters**	NIEHS	(919) 541-3355
Technical Information	Ms. J. Chase	NCI	(301) 496-1152
Public Information	Mr. S. d'Arazien	NTP	(919) 541-3991

*Addresses: National Cancer Institute, Bethesda, M.D. 20205; National Institute of Environmental Health Sciences Research Triangle Park, N.C. 27709; National Library of Medicine, Bethesda, Maryland 20014; National Toxicology Program, Research Triangle Park, N.C. 27709; National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226; National Center for Toxicological Research, Jefferson, Arkansas 72079.

**Acting Program Leader

FIGURE 2



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Toxicology Research and Testing Overview

Toxicology testing within NTP can be placed into three major programs: cellular and genetic toxicology, carcinogenesis, and general toxicology. For descriptive purposes some areas of toxicology are arbitrarily assigned to one of the three programs, even though these areas interact extensively with other programs. An illustration of cross program interaction is the utility of *Salmonella* mutation assays (listed within the genetic toxicology section) to the carcinogenesis program. Table 2 depicts the major segments of the three testing programs and these interrelationships.

The major test initiatives for FY 1981 are summarized below (descriptions of specific program activities are detailed in the next section).

A continuing area of major testing emphasis is genetic toxicology. NTP strategy for FY 1981 is to maintain the rate of *in vitro* microbial (*Salmonella*) mutagenesis testing at 300 chemical starts, to increase parallel testing in cultured mammalian cells to 50 chemicals, and to increase Phase II testing utilizing *Drosophila* systems to a rate of 60 chemicals per year. All chemicals selected for the two-year carcinogenesis bioassay and testing in the general toxicologic screen will be first tested in one or both of the *in vitro* genetic toxicity tests.

In carcinogenesis testing the NTP proposes to start 45 new chemicals on the two-year carcinogenicity bioassays in FY 1981. This is about the same as the level achieved in FY 1980. The Program's strategy is to assure that the most important chemicals from a public health point of view are tested and that end results are relevant to the research and regulatory agencies interested in each chemical. Emphasis is being placed on determining whether the experimental design for bioassays can be modified to provide better low dose extrapolation potential for purposes of risk assessment.

A major innovation in the bioassay program was the expansion of the experimental protocol during the prechronic and chronic testing phases to enhance the detection of toxicologic effects other than cancer, e.g., damage to organs such as liver, kidney and lung, neurobehavioral effects and immunoxicity. About two-thirds of chemical bioassays designed in FY 1980 incorporate a broader protocol design. Concurrently, management and supervision of each new bioassay laboratory is assigned to a NTP scientist.

Most chemicals selected for testing by NTP are selected because too little is known about their toxicologic effects and the potential exists for considerable human exposure. The NTP toxicology testing strategy, initiated in FY 1980, is to identify with assurance the major toxic effects for each chemical studied on chronic tests (Table 2). This includes damage to critical targets such as the lungs, liver, immune and nervous systems, as well as the identification of carcinogens and mutagens. Thus, the Phase I tests should result in a core of toxicology data essential to the proper design of more extensive studies. Using the information from the Phase I rodent toxicologic screen and from special studies included in carcinogenesis bioassays, more extensive toxicology testing can be started with increased capabilities to confirm and define in depth those toxicities identified in the screen. Information from chemical disposition studies will provide further insights into possible toxic mechanisms, and aid in setting dose schedules for subchronic and chronic studies. In the area of reproductive and developmental toxicology, emphasis in FY 1981 will be to test for chemical effects on fertility, and postnatal development as well as for teratogenic effects.

The strategy for test developent or validation is to review existing and emerging newer methodologies to determine which may be adequately sensitive and reproducible. Those most likely to offer improvements over older methods are selected and validated. When basic research findings suggest new areas of toxicology testing, NTP undertakes the appropriate methods develpment and validation. Examples of existing methodology that are being examined for modification are techniques used to detect heritable genetic effects, impaired kidney and pulmonary function, and neurobehavioral toxicity; new areas of methods development and validation include behavioral teratology, immunotoxicology, and short-term tests for presumptive carcinogenic potential.

Validation of test methods is a two-stage process. First, does the procedure yield test results that are reproducible within and between laboratories? Second, does the test predict for toxic potential in humans? The latter requires that NTP pay close attention to the results of human epidemiological studies that may correlate with test results.

The NTP approach to testing will be directed to developing new or better test methods. This is not an indication of flaws in traditional toxicology or regulatory test requirements but reflects an area of science with rapidly expanding boundaries of knowledge. Thus, it necessary that NTP have a planned strategy to validate possible alternative that may be more reliably performed, yield new toxicologic data, yield results relevant to human disease, or develop a testing approach that produces equivalent results in a faster or more economical manner. NTP test results often impact on regulatory or public health issues and thus, NTP will constantly attempt to meld its innovative approaches with "standard" methods in a manner that ensures results that can be used to meet regulatory and public health needs.

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TABLE 2

NTP's Interactive Testing Phases

Program Area	Phase I Identify Toxic Potential	Phase II Corroborate Toxic Effect	Phase III Confirm and Define Toxicity	Phase IV Scientific and Public Health Assessment
Genetic Toxicology	*Salmonella* assay; mammalian cell culture	*Drosophila* SPP	Mammalian assays (mouse heritable translocation)[b]	Total Evaluation of all Data
General Toxicology	Rodent toxicology	Confirmation of organ system toxicities[a]	In-depth characterization; specific toxic effects[a]	(Publication and Dissemination of Information)
Carcinogenesis	Cell culture transformation[b]	Short-term *in vivo* (mouse lung adenoma)[b]	Two-year rodent bioassays	

[a] Validation Phase

[b] Some in Test Validation

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CELLULAR AND GENETIC TOXICOLOGY

The objectives of NTP programs in cellular and genetic toxicology are to develop, evaluate, and implement short-term *in vivo* and *in vitro* systems to detect carcinogenic, mutagenic and toxic effects of chemicals and to perform studies designed to understand the causes of these responses. Most animal test systems are time consuming and expensive, therefore, the development and scientific understanding of short-term assays play a key role in fulfilling the mission of the NTP. These programs will utilize a number of complementary tests of toxic, mutagenic, and carcinogenic potential to provide useful predictive information for assessing potential hazard to humans.

Although there is some overlap in methodology and toxic endpoints, the genetic toxicology and cellular toxicology programs are differentiated in this report by the rational that testing, method development and validation activities in genetic toxicology have the primary aim of detecting and characterizing the mutagenic effects of chemicals. The findings, particularly in *Salmonella* tests, may be correlative for the prediction of potential carcinogenicity in higher organisms. Conversely, test systems being developed and utilized in cellular toxicology may include microbial mutagenesis assays but the primary objectives are to predict and detect the carcinogenicity of chemicals.

Genetic Toxicology

Mutagenicity assays identify structural or functional chromosomal or gene DNA perturbations in germinal or somatic cells. Effects in germ cells are important for predicting potential undesriable effects on fertility, the developing fetus, or in generations subsequent to those which received chemical exposure. Somatic mutation may be predictive for physiologic alternations in the exposed person and for the potential induction of cancer.

The strategy for testing is to develop a screening program consisting of three phases or a composite of tests that vary in complexity from simple systems composed of microbial or mammalian cells in culture to *Drosophila* systems, and finally, to specific whole animal mammalian systems. In this strategy, multiple test systems will be used to complement specific deficiencies in individual tests, and to provide a range of biological responses so that the best prediction can be made of detrimental biological effects in humans. The genetic toxicology test program and its interactions with other NTP programs are charted in Table 2.

FY 1980 Accomplishments

The Phase I *Salmonella* mutagenicity assay was established in FY 1979. During FY 1979, three contracts were awarded for testing, and testing of coded chemicals begun. Chemicals on which *Salmonella* testing has been completed through FY 1980 are listed in Table 3. Since a number of these chemicals were tested in more than one laboratory, there were 222 tests completed for the chemicals in Table 3. Of these, 156 (70%) were considered negative, 60 (27%) positive, and 6 (3%) equivocal as to mutagenicity. This assay uses *Salmonella typhimurium* tester strains TA 98, TA 100, TA 1535, and TA 1537, with and without metabolic activation by liver S–9 fractions from polychlorinated biphenyl (Arochlor 1254)–induced rats and hamsters.

The *Salmonella* mutagenicity assay also is being used by four laboratories to independently validate microbial mutagenicity as a screen for chemical carcinogens, using chemicals not identified to the experimenter (coded assays). An additional objective was to determine the correspondence between mutagenicity and *in vivo* bioassay results, and to determine the reproducibility of the assay procedure. (The contract laboratories are conducting assays under a common protocol.) Of 120 coded compunds for which tests have been completed, 70 have been decoded and the results have demonstrated a good correlation between the four participating laboratories as to which compunds are mutagenic. The combined programs are undertaking the testing of all compounds which have been subject to animal carcinogenesis bioassy, using the same batch of chemicals in most cases.

Tests with cultured mammalian cells are another component of Phase I. Unlike bacterial tests which detect only specific gene DNA effects, the mammalian cell assay can also be used to detect chromosome damage. Testing capability was established in FY 1980 in two laboratories for Chinese Hamster Ovary (CHO) cells in culture with and without Arochlor 1254–induced rat liver S–9 fraction. The final protocol to be used by these laboratories is being validated. The endpoints to be measured include chemical induction or mitotic chromosome aberrations and sister chromatid exchanges.

Chemicals that are mutagenic in Phase I assays, together with a selected number of negative chemicals, will be committed to further testing, taking into account such factors as known biological activity or structural relationships of related compounds, the level of human exposure, and gaps in our knowledge of the genetic effects of specific chemical classes.

The Phase II initiative involves the use of the fruit fly, *Drospophila melanogaster*. There is an extraordinary wealth of genetic and biochemical background information on this easily manipulated organism. In addition, it possesses inherent chemical metabolic activation capability, provides more precise information on the types of mutations induced and the time course of induction, and demonstrates heritability of the induced mutations after sexual matings. Both sex-linked recessive lethal mutations and heritable translocations will be measured. Testing capability was established in FY 1980 in three laboratories and testing began in FY 1980 at the rate of 30 chemicals per year. Chemicals initially selected for testing in *Drosophila* are listed in Table 4.

The chemicals that are positive in the Phase II systems will be subjected to testing in whole animal systems. The objectives of these Phase III tests are to obtain information on the types of mutations produced *in vivo*, the heritability and germ cell sensitivity of the effect, the organs involved and dose-response information. Chemicals producing germ cell damage or mutations will be further tested in animal systems to gather information for use in risk assessment. The mouse heritable translocation assay was chosen for study as a Phase III system. Initial efforts begun during FY 1980 have been to select an appropriate mouse strain for use in heritable translocation studies, and to determine the false positive and false negative errors associated with the classification of individual F_1 animals as suspect or non-suspect translocation carriers based upon analysis of fertility test data. The first positive control study with triethylinemelamine began in late FY 1980.

FY 1981 Program Plans

Mutagenesis testing in Phase I and Phase II assays will continue in FY 1981. There will be 300 chemical test starts in the *Salmonella* assay (Table 5). There will be 50 chemical test starts in cultured mammalian cells, and 60 chemical test starts in *Drosophila* in FY 1981. Many of those tested in the latter two assays will be chemicals found to be mutagenic in the microbial assay.

The potential Phase III tests require validation, and the FY 1981 plan is to initiate such efforts in several

laboratories with the mouse heritable translocation assay. Previously, stock selection of an appropriate mouse strain for use in the studies will have been completed, and additional positive control studies with selected chemicals will be initiated. The mouse specific locus assay will be evaluated as an indicator of the effects of chemicals on mammalian germ cells. An in-depth study of the potent mammalian mutagen, ethylnitrosourea, will be initiated along with the testing of another selected chemical(s) for activity in the specific locus assay.

Contracts are being initiated for development of rapid screening tests for the induction of aneuploidy (the development of abnormal numbers of chromosomes) using *Drosophila melanogaster* and the yeast *Saccharomyces cerevisiae.* Aneuploidy contributed significantly to the genetically-based disease burden in human populations, yet the routine mutagenesis tests (*Salmonella, Drosophila* sex-linked recessive lethal, *in vitro* cytogenetics) are not capable of detecting chemicals that will *only* produce aneuploidy. *Drosophila* and yeast were chosen because they are easily manipulated genetically, can provide evidence of aneuploidy, are relatively quick and easy to use, and can be used to measure other genetic endpoints as well. It is anticipated that the development and validation of one *Drosophila* and one yeast aneuploidy system will be put under contract to be awarded in early FY 1981.

Cellular Toxicology

While the previously described genetic systems have demonstrated predictive value in identification of carcinogens, such inferences are made on the basis of correlations. Therefore, other systems based upon biological responses consistent with the neoplastic (tumor) phenotype must be developed and validated. Four systems are in various developmental stages, including the BALB/c 3T3 cell line, Syrian hamster embryo cell cultures, rat hepatocyte cell strains, and retrovirus-infected rat embryo cells. All systems require continued protocol development and assessment of factors affecting quantitative as well as qualitative results. In addition, criteria for qualitative responses to be observed and acceptability of overall test results need to be defined.

FY 1980 Accomplishments

Work related to program objectives, including studies involving BALB/c 3T3 (clone 1–13 of Kakunaga), have required extensive analysis of factors influencing the induction and quantitation of transformed cells. Effort was directed at estimates of toxicity, target cell density and calculation of transformation frequency as foci/viable cell. Attempts were made to correlate *in vitro* anchorage-independent growth (cells that lose the need to adhere to a substrate) and *in vivo* tumorigenicity with the progression of Type III foci in cell passage, but a quantitative relationship was not seen. The results of metabolic activation studies for conversion of a putative procarcinogen to a carcinogen suggest that different systems will be needed for different chemical classes of procarcinogens. While the results of testing 60 coded samples revealed a good correlation of morphologic transformation with known tumorigenicity, the problems of metabolic activation require further study.

Syrian hamster cell studies required the identification of suitable primary cell cultures, and assays of metabolic activation, including the use of hepatocytes in cocultivation experiments. Assays of a series of coded chemicals have been initiated. Rat hepatocytes have been evaluated as an assay system for induction of DNA repair, and phenotypic transformation. Growth of chemically-treated cells in agar has shown a high correlation with tumorigenicity and this therefore appears to be a suitable endpoint. Fischer rat embryo cells infected with Rauscher leukemia virus have shown transformation with a variety of procarcinogens without addition of an exogenous metabilic activation system. Transformation could be observed within 4–6 weeks after treatment; other protocols which significantly decrease this time are being developed. Assays of 59 coded compounds have been completed and the results are in the final phase of analysis.

Additionally, a genetic assay system is being evaluated and validated for its usefulness as a prescreen for potential chemical carcinogens. The L5178Y mouse lymphoma cell (Tk^+/-locus) system is being evaluated as to its usefulness and reliability as a prescreen for potential chemical carcinogens, and to determine the reproducibility of the assay procedure between two laboratories. Decoding and evaluation of approximately 30 compounds, tested by both laboratories, are in progress.

The first phase of an international collaborative study for the evaluation of short-term assay systems for predicting chemical carcinogenicity was completed in late FY 1979. The toxicological profiles of 42 coded carcinogens and non-carcinogens were determined in up to 35 short-term bioassays (FY 1980 Annual Plan). Decoding was carried out and a workshop held in early FY 1980 to compare and evaluate results and draw conclusions on the performance of the various assays. Preliminary results and conclusions were presented subsequently at open meetings. Preliminary conclusions are:

1. This study confirms that there are short-term tests that can be used to predict carcinogenic activity but no single assay or battery of assays were readily apparent as the best-suited for this purpose.

2. Reliable data from any assay system is dependent upon the investigator's thorough understanding of the system used, awareness of its pitfalls, and careful conduct of experiments.

3. Nearly all assays produced both false negatives and false positives. Therefore, to include any assay in a battery of tests will require a trade off between these two classes of errors.

4. Strong evidence for the use of a test battery was obtained (e.g., with hexamethylphosphoramide, a rodent carcinogen, bacterial results were largely negative in both repair and mutation assays, and yet results in eukaryotic systems from yeast to whole animals were positive).

5. Recommendations on test batteries will have to await a clear definition of their application and the relative importance of false positive and negative results.

FY 1981 Program Plans

Based upon the results described for the four developmental cell culture systems—the BALB/c 3T3 cell line, Syrian hamster embryo cell cultures, rat hepatocyte cells, and retrovirus-infected rat embryo cells, as well as the genetic system (L5178Y mouse lymphoma cell)—the FY 1981 program plans in the area of cellular toxicology will combine three primary elements. First, there will be an initiation of protocol development and a systematic dual laboratory comparison of the primary *candidate* mammalian cell transformation assay system. Second, studies of *in vivo* carcinogenesis systems will be directed toward development of Phase III short-term, whole animal tests.

Third, NTP will support the development of assay systems which promise additional advantages in accuracy, precision or fidelity but which are not sufficiently defined to be validated as toxicologic or carcinogenic tests. It is important that test methods which reflect the evolution in understanding the mechanisms of toxic

and carcinogenic effects continue to be sought, particularly those which utilize human cells. The problems associated with the extrapolation of the results of *in vitro* and short-term assays to human populations will also be addressed.

Finally, in the international collaborative study for the evaluation of short-term assay systems for predicting chemical carcinogenesis, an in-depth analysis of the data base will be completed, and the discussions of the results and conclusions of the study will be published in book form and in the scientific literature. Resources permitting, additional test data will be obtained in support of further evaluating certain assays. A complete evaluation of these systems is important for at least two reasons. First, several systems involve mammalian cells which are closely related to the cells in which we are ultimately interested (human cells). Second, several systems detect endpoints other than gene mutations and may yield meaningful results on carcinogens which act via other genetic or epigenetic mechanisms.

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TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
1	Acetamide	(-)	60-35-5	10375-A
2	Aniline	(-)	62-53-3	10379-H
3	Azobenzene	(+,+)	103-33-3	10499-L
4	Azodicarbonamide	(+)	123-77-3	10085-W
5	AF-2	(+,+)	3688-53-7	10831-E
6	Benzaldehyde	(-)	100-52-7	10087-A
7	Benzo(a)pyrene	(+,+)	50-32-8	10353-C
8	Benzofuran	(-)	271-89-6	10058-F
9	Benzyl salicylate	(-,-)	118-58-1	10545-L
10	Beta-Methylumbelliferone	(-)	90-33-5	10437-G
11	Beta-Picoline	(-)	108-99-6	10530-J
12	Biphenyl	(-,-)	92-52-4	10444-D
13	Bisphenol A	(-,-,-)	80-05-7	10034-Y
14	Boric acid	(-)	10043-35-3	10035-D
15	Bromobenzene	(-)	108-86-1	10060-G
16	Bromoform	(?)	75-25-2	10396-V
17	Cacodylic acid	(-)	75-60-5	10401-J
18	Calcium chromate	(+,+)	13765-19-0	10827-V
19	Carbon disulfide	(-,-)	75-15-0	10014-H
20	Catechol	(-,-)	120-80-9	10094-W
21	Chloral hydrate	(+)	302-17-0	10609-C
22	Chlorobenzene	(-,-)	108-90-7	10528-H
23	Choline chloride	(-)	67-48-1	10846-G
24	Cis-Stilbene	(-)	645-49-8	10657-H
25	Crotonaldehyde	(+)	4170-30-3	10252-S
26	Cyanuric acid	(-)	108-80-5	10526-A
27	Cyclohexanol	(-)	108-93-0	10529-L
28	Cyclohexanone	(-,-)	108-94-1	10064-X
29	Cyclophosphamide	(+,+)	50-18-0	10351-T
30	D-Limonene dimercaptan	(-,-,-)	4802-20-4	10841-L

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
31	Di(2-ethylhexyl) phthalate	(-,-)	117-81-7	10188-J
32	Di(2-ethylhexyl)adipate	(-,-)	103-23-1	10497-E
33	Di-n-butylamine	(-)	111-92-2	10535-E
34	Diacetone acrylamide	(-)	2873-97-4	10719-P
35	Diethanolamine	(-)	111-42-2	10534-A
36	Diethyl carbonate	(-)	105-58-8	10253-W
37	Diethylene glycol dimethyl ether	(-)	111-96-6	10536-H
38	Dimethylamine	(-,-)	124-40-3	10569-T
39	Dimethylcarbamoyl chloride	(+,+)	79-44-7	10416-L
40	Dimethylcyanamide	(-,-)	1467-79-4	10684-V
41	Dimethylformamide	(-)	68-12-2	10256-H
42	Diphenyl oxide	(-)	101-84-8	10491-F
43	Diphenylhydantoin	(-,-)	57-41-0	10156-D
44	Ethylene glycol	(-)	107-21-1	10118-E
45	Ethylene thiourea	(-)	96-45-7	10466-C
46	Ethylenediamine	(+W)	107-15-3	10190-K
47	Eugenol	(-)	97-53-0	10468-J
48	Ferrocene	(?)	102-54-5	10495-W
49	Formaldehyde	(+,+)	50-00-0	10002-S
50	Furfural	(-,?)	98-01-1	10120-F
51	Gallic acid	(-,-)	149-91-7	10599-S
52	Glycerol	(-,-,-)	56-81-5	10870-N
53	Glycine	(-,-)	56-40-6	10877-J
54	Hematoxylin	(-)	517-28-2	10044-B
55	Hexabromobiphenyl	(-)	36355-01-8	10021-E
56	Hexachlorobenzene	(-)	118-74-1	10546-R
57	Hexachlorobutadiene	(-)	87-68-3	10124-W
58	Hexachlorocyclopentadiene	(-)	77-47-4	10125-A
59	Hexachloroethane	(-,-)	67-72-1	10126-E
60	Hexachlorophene	(-)	70-30-4	10387-R
61	Hydrazobenzene	(+)	122-66-7	10872-P

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
62	Hydroquinone	(-)	123-31-9	10022-H
63	Hydroquinone dimethyl ether	(-)	150-78-7	10603-D
64	Hydroquinone monomethyl ether	(-)	150-76-5	10602-Y
65	Lithium chloride	(-)	7447-41-8	10743-P
66	M-Chlorophenol	(-)	108-43-0	10522-J
67	M-Cresol	(-)	108-39-4	10521-F
68	M-Xylene	(-)	108-38-3	10520-C
69	Mannitol	(-)	69-65-8	10386-L
70	Methacrylic acid	(-)	79-41-4	10415-H
71	Methylhydrazine	(-)	60-34-4	10374-W
72	Morpholine	(-)	110-91-8	10533-W
73	N-Butyl-p-aminobenzoate	(-)	94-25-7	10448-T
74	N-Nitrosodimethylamine	(+,+)	62-75-9	10657-T
75	N-Nitrosopiperidine	(+)	100-75-4	10656-P
76	N,N-Dimethylurea	(-)	96-31-1	10643-J
77	Nickelocene	(-)	1271-28-9	10675-R
78	Nitrofurantoin	(+)	67-20-9	10382-W
79	O-Aminophenol	(+,+W,+)	95-55-6	10458-C
80	O-Chlorophenol	(-)	95-57-8	10459-F
81	O-Cresol	(-)	95-48-7	10455-P
82	O-Methoxyphenol	(-,-)	90-05-1	10436-D
83	O-Xylene	(-)	95-47-6	10454-K
84	Oxalic acid	(-)	144-62-7	10049-C
85	P-Anisidine	(-)	104-94-9	10501-P
86	P-Chlorophenol	(-)	106-48-9	10510-T
87	P-Cresol	(-)	106-44-5	10509-W
88	P-Nitrophenol	(-)	100-02-7	10142-E
89	P-Quinone	(-)	106-51-4	10162-V
90	P-Xylene	(-)	106-42-3	10508-S
91	Pentachlorobenzene	(-)	608-93-5	10646-W
92	Pentachloronitrobenzene	(-)	82-68-8	10033-V

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
93	Pentachlorophenol	(-)	87-86-5	10429-G
94	Phenyl salicylate	(-,-)	118-55-8	10544-H
95	Picric acid	(+)	88-89-1	10432-L
96	Piperazine	(-)	110-85-0	10531-N
97	Piperonal	(-)	120-57-0	10552-H
98	Propiolactone	(+,+)	57-57-8	10370-F
99	Pyridine	(-)	110-86-1	10532-S
100	Quinoline	(+)	91-22-5	10441-R
101	Resorcinol	(-)	108-46-3	10163-Y
102	Rhodanine	(-)	141-84-4	10595-C
103	Semicarbazide hydrochloride	(-)	563-41-7	10631-T
104	Sodium azide	(+)	26628-22-8	10164-D
105	Sodium fluoride	(-)	7681-49-4	10746-C
106	Sodium ligninsulfonate	(-)	8061-51-6	10750-K
107	Sodium phosphate, dibasic	(-,-)	7558-79-4	10933-S
108	Sodium ricinoleate	(-,-)	5323-95-5	10731-Y
109	Sodium thioglycolate	(-)	367-51-1	10613-K
110	Streptomycin sulfate	(+,-)	3810-74-0	10932-N
111	Terephthalic acid	(-)	100-21-0	10479-W
112	Tetrachloroethylene	(-)	127-18-4	10176-T
113	Tetrachlorophthalic anhydride	(-)	117-08-8	10540-S
114	Tetraethyllead	(-)	78-00-2	10031-L
115	Thiocarbanilide	(-,-)	102-08-9	10493-W
116	Toluene	(-)	108-88-3	10009-V
117	Trans-Stilbene	(-)	103-30-0	10498-H
118	Tributoxyethyl phosphate	(-)	78-51-3	10414-E
119	Tributyl borate	(-,-)	688-74-4	10659-R
120	Tricresyl phosphate	(-,-)	1330-78-5	10277-D
121	Triethanolamine	(-)	102-71-6	10496-A
122	Triphenylphosphine	(-)	603-35-0	10645-S
123	1-Aziridineethanol	(+)	1072-52-2	10671-A

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
124	1-Fluoro-2,4-dinitrobenzene	(+)	70-34-8	10388-V
125	1,1-Dichloroethylene	(-)	75-35-4	10109-A
126	1,2-Dichlorobenzene	(-)	95-50-1	10456-T
127	1,2-Dichloropropane	(?)	78-87-5	10111-C
128	1,2-Propylene glycol	(-,-)	57-55-6	10369-H
129	1,2,3-Trichlorobenzene	(-)	87-61-6	10083-J
130	1,2,3,4-Tetrachlorobenzene	(-)	634-66-2	10652-N
131	1,2,3,5-Tetrachlorobenzene	(-)	634-90-2	10653-S
132	1,2,4-Trichlorobenzene	(-)	120-82-1	10187-F
133	1,3-Dichlorobenzene	(-)	541-73-1	10626-F
134	1,3-Dioxane	(+W)	505-22-6	10622-P
135	1,3,5-Trichlorobenzene	(-)	108-70-3	10524-S
136	1,4-Dichlorobenzene	(-)	106-46-7	10038-P
137	1,4-Dioxane	(-)	123-91-1	10568-P
138	2-Aminoanthracene	(+,+,+)	613-13-8	10912-X
139	2-Biphenylamine	(+)	90-41-5	10438-K
140	2-Chloronitrobenzene	(+W)	88-73-3	10431-N
141	2-Fluorobenzoyl chloride	(+)	393-52-2	10615-T
142	2-Nitro-a,a,a-trifluorotoluene	(-)	384-22-5	10614-P
143	2-Nitropropane	(+,+)	79-46-9	10417-R
144	2,3-Dibromo-1-propanol	(+)	96-13-9	10016-R
145	2,3-Dichloronitrobenzene	(?)	3209-22-1	10721-R
146	2,3-Dichlorophenol	(-)	576-24-9	10636-N
147	2,3,5,6-Tetrachloronitrobenzene	(?)	117-18-0	10541-W
148	2,4-D isooctyl ester	(-)	25168-26-7	10908-N
149	2,4-Diaminophenol dihydrochloride	(+)	137-09-7	10106-N
150	2,4-Dichloronitrobenzene	(+)	611-06-3	10648-E
151	2,4-Dichlorophenol	(-)	120-83-2	10557-D
152	2,4-Dinitrotoluene	(+)	121-14-2	10558-G
153	2,4,5-T isooctyl ester	(-)	25168-15-4	10906-F
154	2,4,6-Trichlorophenol	(-)	88-06-2	10430-E

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 3

CHEMICALS TESTED IN SALMONELLA MUTAGENICITY ASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	RESULT*	CAS NO.	NTP NO.
155	2,5-Dichlorophenol	(-)	583-78-8	10637-S
156	2,6-Dichlorophenol	(-)	87-65-0	10427-Y
157	2,6-Dimethyl morpholine	(+)	141-91-3	10903-T
158	2'-Methyl-4-dimethylaminoazobenzene	(+W,-)	3731-39-3	10902-P
159	3-Amino-a,a,a-trifluorotoluene	(-)	98-16-8	10470-K
160	3-Methylcholanthrene	(+,+)	56-49-5	10899-H
161	3-Nitro-a,a,a-trifluorotoluene	(-)	98-46-4	10471-P
162	3,3'-Dimethoxybenzidine	(+,+,+)	119-90-4	10895-S
163	3,4-Dichloronitrobenzene	(+)	99-54-7	10474-C
164	3,4-Dichlorophenol	(-)	95-77-2	10461-G
165	3,5-Dichlorophenol	(-)	591-35-5	10639-A
166	4-Biphenylamine	(+,+)	92-67-1	10445-G
167	4-Chloro-a,a,a-trifluorotoluene	(-)	98-56-6	10472-T
168	4-Chloro-3-nitro-a,a,a-trifluorotoluene	(-)	121-17-5	10559-K
169	4-Chloro-3,5-dinitro-a,a,a-trifluorotoluene	(-)	393-75-9	10616-X
170	4-Chloronitrobenzene	(+,+)	100-00-5	10478-S
171	4-Hydroxyacetanilide	(-)	103-90-2	10127-H
172	4,4'-Methylenebis(2-chloroaniline)	(+)	101-14-4	10484-J

* (-) = negative, (+) = positive, (?) = equivocal, (+W) = weakly positive. There may be from one to three tests reported for each compound.

TABLE 4

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN DROSOPHILA MUTAGENICITY ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
1	Calcium chromate	13765-19-0	10827-V
2	Di(2-ethylhexyl) phthalate	117-81-7	10188-J
3	Dimethylcarbamoyl chloride	79-44-7	10416-L
4	Ethylenediamine	107-15-3	10190-K
5	Ferrocene	102-54-5	10495-W
6	Hexachlorocyclopentadiene	77-47-4	10125-A
7	Hydrazobenzene	122-66-7	10872-P
8	N-Nitrosodimethylamine	62-75-9	10857-T
9	Nitrofurantoin	67-20-9	10382-W
10	P-Nitrophenol	100-02-7	10142-E
11	Picric acid	88-89-1	10432-L
12	Propiolactone	57-57-8	10370-F
13	Quinoline	91-22-5	10441-R
14	Streptomycin sulfate	3810-74-0	10932-N
15	Thiocarbanilide	102-08-9	10493-N
16	1,3-Dioxane	505-22-6	10622-P
17	1,3,5-Trichlorobenzene	108-70-3	10524-S
18	2-Chloronitrobenzene	88-73-3	10431-H
19	2-Nitropropane	79-46-9	10417-R
20	2,3-Dichloronitrobenzene	3209-22-1	10721-R
21	2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	10157-G
22	2,4-Diaminophenol dihydrochloride	137-09-7	10106-N
23	2,4-Dichloronitrobenzene	611-06-3	10648-E
24	2,4-Dichlorophenoxyacetic acid	94-75-7	10451-T
25	2,4-Dinitrotoluene	121-14-2	10558-G
26	2,4,5-Trichlorophenoxyacetic acid	93-76-5	10447-P
27	2,6-Dimethyl morpholine	141-91-3	10903-T
28	3,4-Dichloronitrobenzene	99-54-7	10474-C
29	4-Biphenylamine	92-67-1	10445-G
30	4-Chloronitrobenzene	100-00-5	10478-S

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
1	Adipamide	628-94-4	10825-L
2	Agaritine	2757-90-6	10713-R
3	Allyl glycidyl ether	106-92-3	10824-H
4	Allyl isothiocyanate	57-06-7	10367-A
5	Allyl isovalerate	2835-39-4	10717-G
6	Amiben	133-90-4	10823-E
7	Ampicillin trihydrate	7177-48-2	10832-H
8	Azinphosmethyl	86-50-0	10424-L
9	Benzidine	92-87-5	10446-W
10	Benzoin	119-53-9	10550-A
11	Benzyl acetate	140-11-4	10591-K
12	Benzyl alcohol	100-51-6	10059-J
13	Beta-Cadinene	523-47-7	10091-J
14	Bis(2 chloro-1-methylethyl) ether	108-60-1	10523-N
15	Bromodichloromethane	75-27-4	10397-Y
16	Butyl benzyl phthalate	85-68-7	10422-E
17	Butyl(2,4-dichlorophenoxy) acetate	94-80-4	10830-A
18	Butyl(2,4,5-trichlorophenoxy) acetate	93-79-8	10829-D
19	Butylated hydroxytoluene	128-37-0	10575-K
20	C I Acid Red 114	6459-94-5	10286-G
21	C I Pigment Red 23	6471-49-4	10210-D
22	C I Pigment Red 3	2425-85-6	10209-F
23	C I Vat Yellow 4	128-66-5	10576-P
24	Cadmium chloride	10108-64-2	10828-Y
25	Cadmium oxide	1306-19-0	10212-K
26	Caffeine	58-08-2	10036-G
27	Calcium cyanamide	156-62-7	10606-P
28	Carbendazim	10605-21-7	10826-M
29	Carbromal	77-65-6	10408-L
30	Carvone	99-49-0	10093-S

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
31	Chloral	75-87-6	10404-W
32	Chlorambucil	305-03-3	10850-R
33	Chlordane	12789-03-6	10849-T
34	Chlordecone	143-50-0	10097-H
35	Chlorobenzilate	510-15-6	10088-E
36	Chlorodibromomethane	124-48-1	10570-R
37	Chloropicrin	76-06-2	10848-P
38	Chlorothalonil	1897-45-6	10692-V
39	Chlorothen	148-65-2	10192-T
40	Chlorowax 40	63449-39-8	10062-P
41	Chlorowax 500C	63449-39-8	10063-T
42	Chlorpheniramine maleate	113-92-8	10537-L
43	Chlorpromazine hydrochloride	69-09-0	10101-T
44	Chlorpropamide	94-20-2	10847-K
45	Cineol	470-82-6	10015-L
46	Cis-Methyl oleic acid ester	112-62-9	10146-V
47	Clonitralid	1420-04-8	10682-L
48	Copper acetoarsenite	12002-03-8	10229-W
49	Coumarin	91-64-5	10104-F
50	Croton oil	8001-28-3	10845-D
51	Curcumin	458-37-7	10105-J
52	Cytarabine	147-94-4	10843-V
53	Cytembena	21739-91-3	10778-H
54	Cytoxal alcohol	4465-94-5	10842-R
55	D-Limonene	5989-27-5	10071-T
56	D-Phenylalanine	673-06-3	10153-R
57	Dacarbazine	4342-03-4	10840-H
58	Decabromodiphenyl oxide	1163-19-5	10672-E
59	Di(p-ethylphenyl)dichloroethane	72-56-0	10394-L
60	Di(2-ethylhexyl)adipate	103-23-1	10497-E
61	Diallyl phthalate	131-17-9	10576-X

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
62	Diarylanilide yellow	6358-85-6	10839-K
63	Dibenzo-p-dioxin	262-12-4	10607-T
64	Dibromodulcitol	10318-26-0	10836-G
65	Dibromomannitol	488-41-5	10837-O
66	Dibutyltin diacetate	1067-33-0	10670-W
67	Dichlorodiphenylethylene	72-55-9	10393-H
68	Dichloromethotrexate	528-74-5	10836-Y
69	Dicofol	115-32-2	10835-V
70	Dieldrin	60-57-1	10834-R
71	Diesel fuel marine	DIESEL FUEL	10805-W
72	Diethyl phthalate	84-66-2	10112-F
73	Diglycidyl resorcinol ether	101-90-6	10492-J
74	Dimenhydrinate	523-87-5	10194-C
75	Dimethoate	60-51-5	10888-W
76	Dimethoxane	828-00-2	10114-N
77	Dimethyl hydrogenphosphite	868-85-9	10663-A
78	Dimethyl methylphosphonate	756-79-6	10660-N
79	Dimethyl morpholinophosphonate	597-25-1	10641-C
80	Dimethyl sulfoxide	67-68-5	10116-W
81	Dimethyl terephthalate	120-61-6	10553-L
82	Dimethyloldihydroxyethyleneurea	1854-26-8	10205-P
83	Dimethylvinyl chloride	513-37-1	10623-T
84	Dioxathion	78-34-2	10411-S
85	Diphenhydramine hydrochloride	147-24-0	10040-R
86	Direct Black 114	61703-05-7	10887-S
87	Direct Blue 1	2610-05-1	10287-K
88	Direct Blue 15	2429-74-5	10701-A
89	Direct Blue 218	28407-37-6	10249-L
90	Direct Blue 25	2150-54-1	10885-J
91	Direct Blue 53	314-13-6	10884-F
92	Direct Blue 6	2602-46-2	10883-C

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
93	Direct Brown 95	16071-86-6	10682-X
94	Direct Red 2	992-59-6	10668-V
95	Doxylamine	469-21-6	10195-F
96	Dulcin	150-69-6	10881-T
97	DMA-4 herbicide	2008-39-1	10880-P
98	Endosulfan	115-29-7	10879-S
99	Endrin	72-20-8	10391-A
100	Erythromycin stearate	643-22-1	10656-E
101	Ethyl acrylate	140-88-5	10594-X
102	Ethyl tellurac	20941-65-5	10777-E
103	Ethyl-3-methyl-3-phenylglycidate	77-83-8	10409-R
104	Ethylene chlorohydrin	107-07-3	10517-W
105	Fenthion	55-38-9	10362-F
106	Fluorescein, sodium	518-47-8	10624-X
107	Formulated fenaminosulf	140-56-7	10593-T
108	Furan	110-00-9	10119-H
109	Furfuryl alcohol	98-00-0	10121-J
110	Furosemide	54-31-9	10068-H
111	Geranyl acetate	105-87-3	10507-N
112	Gibberellic acid	77-06-5	10407-H
113	Glycol (Polysorbate 80)	9005-65-6	10122-N
114	Guanazole	1455-77-2	10876-F
115	Heptachlor	76-44-8	10875-C
116	Hexachlorobutadiene	87-68-3	10124-W
117	Hexamethyl-p-rosaniline	548-62-9	10008-R
118	Hexamethylmelamine	645-05-6	10874-X
119	Hexanamide	628-02-4	10873-T
120	Hexylresorcinol	136-77-6	10588-F
121	Hydrochlorothiazide	58-93-5	10029-K
122	Hydroxyurea	127-07-1	10871-K
123	HC Yellow 4	52551-67-4	10123-S

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
124	Indomethacin	53-86-1	10129-R
125	Iodoform	75-47-8	10398-D
126	Isoamyl nitrite	110-46-3	10870-G
127	Isobutyl nitrite	542-56-3	10869-J
128	Isophorone	78-59-1	10070-P
129	Isoproterenol hydrochloride	51-30-9	10130-N
130	Lasiocarpine	303-34-4	10868-F
131	Lead dimethyldithiocarbamate	19010-66-3	10772-J
132	Lead dioxide	1309-60-0	10131-S
133	Lindane	58-89-9	10865-T
134	M-Nitrotoluene	99-08-1	10864-P
135	Malaoxon	1634-78-2	10686-D
136	Malathion	121-75-5	10563-V
137	Maleic hydrazide diethanolamine	5716-15-4	10734-K
138	Malonaldehyde	542-78-9	10627-J
139	Mercaptobenzothiazole	149-30-4	10073-C
140	Mercuric chloride	7487-94-7	10133-A
141	Methapyrilene	91-80-5	10135-H
142	Methdilazine	1982-37-2	10203-G
143	Methoxychlor	72-43-5	10863-K
144	Methyl coumarin	92-48-8	10136-L
145	Methyl methacrylate	80-62-6	10410-V
146	Methyl parathion	298-00-0	10608-X
147	Mexacarbate	315-18-4	10610-Y
148	Mirex	2385-85-5	10699-X
149	Monochloroacetic acid	79-11-8	10138-V
150	Monosodium methane arsenate	1639-59-4	10139-Y
151	Monuron	150-68-5	10600-R
152	Myleran	55-98-1	10861-D
153	N-(1-Naphthyl)ethylenediamine dihydrochloride	1465-25-4	10683-R
154	N-Butyl chloride	109-69-3	10089-H

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
155	N-Hexane	110-54-3	10189-N
156	N-Methyl-p-aminophenol sulfate	55-55-0	10858-X
157	N-Nitrosodiethanolamine	1116-54-7	10143-H
158	N-Nitrosodimethylamine	62-75-9	10857-T
159	N-Phenyl-p-phenylenediamine	101-54-2	10855-K
160	N-Phenylhydroxylamine	100-65-2	10154-V
161	N,N-Dimethyl-p-nitrosoaniline	138-89-6	10854-G
162	N,N'-Diethylthiourea	105-55-5	10503-X
163	Naphthalene	91-20-3	10046-P
164	Navy fuels JP-5	NAVY FUELS	10140-H
165	Neohesperidin dihydrochalcone	20702-77-6	10215-X
166	Nithiazide	139-94-6	10853-D
167	Nitrobenzene	98-95-3	10141-A
168	Nitroethane	79-24-3	10852-Y
169	Nitrofurazone	59-87-0	10047-T
170	Nitromethane	75-52-5	10851-V
171	O-Methylhydroxylamine	67-62-9	10137-R
172	O-Nitroanisole	91-23-6	10211-G
173	O-Nitrotoluene	88-72-2	10946-L
174	O-Phenylphenol	90-43-7	10439-P
175	O-Toluidine hydrochloride	636-21-5	10654-W
176	O,P'-DDD	53-19-0	10945-H
177	Octachlorodibenzodioxin	3268-87-9	10145-R
178	Oxytetracycline hydrochloride	2058-46-0	10080-X
179	P-Chloroaniline	106-47-8	10100-P
180	P-Nitroaniline	100-01-6	10217-F
181	P-Nitrosodiphenylamine	156-10-5	10605-K
182	P-Nitrotoluene	99-99-0	10944-E
183	P-Tolylurea	622-51-5	10943-A
184	Palladium chloride (2+)	7647-10-1	10148-D
185	Parathion	56-38-2	10942-W

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
186	Penicillin VK	132-98-9	10581-D
187	Pentachloroanisole	1825-21-4	10024-R
188	Pentachloroethane	76-01-7	10149-G
189	Pentaerythritol tetranitrate	78-11-5	10150-E
190	Phenacetin	62-44-2	10378-L
191	Phenazopyridine hydrochloride	136-40-3	10587-C
192	Phenbenzamine	961-71-7	10201-Y
193	Phenesterin	3546-10-9	10940-N
194	Phenformin	114-86-3	10939-R
195	Pheniramine	86-21-5	10197-N
196	Phenol	108-95-2	10076-N
197	Phenolphthalein	77-09-8	10050-Y
198	Phenoxybenzamine hydrochloride	63-92-3	10938-L
199	Phenylbutazone	50-33-9	10354-F
200	Phenylmercuric acetate	62-38-4	10134-E
201	Phosphamidon	13171-21-6	10763-F
202	Photodieldrin	13366-73-9	10937-H
203	Phthalamide	88-96-0	10433-R
204	Phthalic anhydride	85-44-9	10421-A
205	Pichloram	1918-02-1	10155-Y
206	Piperonyl butoxide	51-03-6	10358-M
207	Piperonyl sulfoxide	120-62-7	10554-R
208	Polyvinylchloride latex	9002-86-2	10218-J
209	Prednisone	53-03-2	10936-E
210	Probenecid	57-66-9	10160-L
211	Promethazine	60-87-7	10202-D
212	Propyl gallate	121-79-9	10564-Y
213	Pyrazinamide	98-96-4	10916-N
214	Pyrilamine	91-84-9	10198-S
215	Pyrimethamine	58-14-0	10904-X
216	Resorcine Blue	1787-53-7	10935-A

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
217	Rotenone	83-79-4	10420-W
218	Sodium (2-ethylhexyl)alcohol sulfate	126-92-1	10572-Y
219	Sodium cyanurate	2624-17-1	10710-E
220	Sodium dichloroisocyanurate	2893-78-9	10165-G
221	Sodium diethyldithiocarbamate	148-18-5	10597-J
222	Sodium dodecyl sulfate	151-21-3	10604-G
223	Sodium iodomethanesulfonate	126-31-8	10934-W
224	Sodium xylenesulfonate	1300-72-7	10184-T
225	Stearatochromic chloride complex	15242-96-3	10219-N
226	Succinic acid 2,2-dimethylhydrazide	1596-84-5	10685-Y
227	Sulfacetamide	144-80-9	10931-J
228	Sulfallate	95-06-7	10452-D
229	Sulfamethazine	57-68-1	10056-X
230	Sulfanilamide	63-74-1	10930-F
231	Tert-Butyl alcohol	75-65-0	10402-N
232	Tetrachlordiphenylethane	72-54-8	10392-E
233	Tetrachlorvinphos	961-11-5	10929-H
234	Tetracycline hydrochloride	64-75-5	10381-S
235	Tetraethylthiuram disulfide	97-77-8	10291-V
236	Tetrahydrofuran	109-99-9	10170-V
237	Tetramethyllead	75-74-1	10403-S
238	Thenyldiamine	91-79-2	10196-J
239	Thonzylamine	91-85-6	10199-W
240	Titanium ferrocene	1271-19-8	10174-K
241	Tolazamide	1156-19-0	10928-E
242	Tolbutamide	64-77-7	10927-A
243	Toluene diisocyanate	584-84-9	10638-W
244	Toxaphene	8001-35-2	10926-W
245	Trichlorfon	52-68-6	10360-X
246	Trichlorofluoromethane	75-69-4	10925-S
247	Trifluralin	1582-09-8	10924-N

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
248	Trimellitic anhydride	552-30-7	10026-Y
249	Trimethylthiourea	2489-77-2	10708-D
250	Tripelennamine	91-81-6	10200-V
251	Tris(2-chloroethyl) phosphate	115-96-8	10178-C
252	Tris(2-ethylhexyl) phosphate	78-42-2	10413-A
253	Urea	57-13-6	10922-F
254	Vinyl cyclohexene dioxide	106-87-6	10179-F
255	Vinylidene fluoride	75-38-7	10180-D
256	Vitamin D	1406-16-2	10181-G
257	Vitamin D3	67-97-0	10182-K
258	Witch hazel	68916-39-2	10183-P
259	Wollastonite calcium silicates	13983-17-0	10027-D
260	Zearalenone	17924-92-4	10770-C
261	Ziram	137-30-4	10590-G
262	Zirconium oxychloride	7699-43-6	10220-K
263	1(2H)-Phthalazinone	119-39-1	10549-D
264	1-(4-Nitrophenylazo)-2-naphthalenamine	3025-77-2	10216-C
265	1-Acetyl-2-picolinoyl hydrazine	17433-31-7	10921-C
266	1-Amino-2,4-dibromoanthraquinone	81-49-2	10084-N
267	1-Nitrobutane	627-05-4	10920-X
268	1-Nitrohexane	646-14-0	10919-A
269	1-Nitropropane	108-03-2	10918-M
270	1-Phenyl-2-thiourea	103-85-5	10500-K
271	1-Phenyl-3-methyl-5-pyrazolone	89-25-8	10434-V
272	1,1,1,2-Tetrachloroethane	630-20-6	10651-J
273	1,1,2,2-Tetrachloroethane	79-34-5	10915-J
274	1,2-Epoxybutane	106-88-7	10066-F
275	1,2-Epoxyhexadecane	7320-37-8	10740-D
276	1,2,3-Trichloropropane	96-18-4	10914-F
277	1,2,3,6,7,8(7,8,9)-Hexachlorodibenzo-p-dioxin (Mix)	HCDD MIX	10790-S
278	1,3-Dichloro-5,5-dimethylhydantoin	118-52-5	10543-E

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
279	1,3-Dichloropropene	542-75-6	10560-W
280	1,4-Diamino-2,6-dichlorobenzene	609-20-1	10647-A
281	1,4-Naphthalenediamine	2243-61-0	10913-C
282	1,8-Dihydroxy-4,5-dinitroanthraquinone	81-55-0	10213-P
283	11-Aminoundecanoic acid	2432-99-7	10785-W
284	2-Amino-4-nitrophenol	99-57-0	10005-E
285	2-Amino-5-nitrophenol	121-88-0	10565-D
286	2-Bromobiphenyl	2052-07-5	10911-T
287	2-Butanone peroxide	1338-23-4	10001-N
288	2-Chloro-p-phenylenediamine sulfate	61702-44-1	10801-F
289	2-Chloro-1,3-butadiene	126-99-8	10573-D
290	2-Chloroethyltrimethylammonium chloride	999-81-5	10669-Y
291	2-Chloromethylpyridine hydrochloride	6959-47-3	10738-C
292	2-Ethoxyethanol	110-80-5	10117-A
293	2-Methyl-1-nitroanthraquinone	129-15-7	10918-P
294	2-Nitropropane	79-46-9	10417-R
295	2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	10722-V
296	2,3,7,8-tetrachlorodibenzo-p-dioxin	1746-01-6	10157-G
297	2,4-D isooctyl ester	25168-26-7	10908-H
298	2,4-Diaminotoluene	95-80-7	10463-P
299	2,4-Dichlorophenoxyacetic acid	94-75-7	10451-Y
300	2,4-Dinitroaniline	97-02-9	10214-T
301	2,4,5-T isobutyl ester	4938-72-1	10907-J
302	2,4,5-T isooctyl ester	25168-15-4	10906-F
303	2,4,5-Trichlorophenoxyacetic acid	93-76-5	10447-P
304	2,4,5-Trimethylaniline	137-17-7	10589-J
305	2,4,6-Trinitrotoluene	118-96-7	10177-X
306	2,5-Dithiobiurea	142-46-1	10905-C
307	2,6-Xylidine	87-62-7	10165-X
308	2,7-Dichlorodibenzo-p-dioxin	33857-26-0	10789-V
309	3-Amino-4-ethoxyacetanilide	17026-81-2	10901-K

TABLE 5

CHEMICALS SCHEDULED FOR TESTING IN FY 1981 IN SALMONELLA MUTAGENESIS ASSAYS

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.
310	3-Amino-9-ethylcarbazole hydrochloride	132-32-1	10579-C
311	3-Bromobiphenyl	2113-57-7	10900-G
312	3-Chloro-p-toluidine	95-74-9	10460-D
313	3-Chloro-2-methylpropene	563-47-3	10632-X
314	3-Chloromethylpyridine hydrochloride	6959-48-4	10739-F
315	3-Nitro-p-acetophenetide	1777-84-0	10689-P
316	3-Sulfolene	77-79-2	10898-E
317	3,3'-Dichlorobenzidine	91-94-1	10897-A
318	3,3'-Dihydroxybenzidine	2373-98-0	10896-W
319	3,3'-Dimethoxybenzidine-4,4'-diisocyanate	91-93-0	10115-S
320	3,3'-Dimethylbenzidine dihydrochloride	612-82-8	10894-N
321	3,4-Dihydrocoumarin	119-84-6	10113-J
322	4-Bromobiphenyl	92-66-0	10893-J
323	4-Chloro-o-phenylenediamine	95-83-0	10892-F
324	4-Chloro-o-toluidine hydrochloride	3165-93-3	10720-L
325	4-Chloro-2-nitroaniline	89-63-4	10208-C
326	4-Nitroanthranilic acid	619-17-0	10649-H
327	4-Vinylcyclohexene	100-40-3	10480-T
328	4,4'-Diphenylmethane diisocyanate	101-68-8	10488-A
329	4,4'-Sulfonyldianiline	80-08-0	10890-X
330	5(6)-Nitrobenzimidazole	94-52-0	10449-X
331	5-Azacytidine	320-67-2	10889-A
332	5-Chloro-o-toluidine	95-79-4	10462-K
333	5-Hydroxytryptophan	56-69-9	10128-L
334	5-Nitro-o-anisidine	99-59-2	10477-N
335	5-Nitroacenaphthene	602-87-9	10644-N

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Carcinogenesis Testing

The two-year carcinogenesis bioassay is still the standard and most definitive method for detecting chemical carcinogens in animals. The test employs two sexes and two species, usually rats and mice, uses multiple dose levels of a chemical, begins at weaning and ends after two years. The results of the bioassay also serve as the reference base for the validation of short-term carcinogenesis assays. Table 6 lists the various phases of the bioassay process in chronological order.

The bioassay has scientific limitations—the data are difficult to use in quantitative estimation of hazard to humans and the findings provide little insight as to carcinogenic mechanism(s). And, until recently, it gave relatively little information about critical toxic effects other than carcinogenesis. However, it should be noted that the standard bioassay was neither designed nor intended to provide such information. Like other biological assays, the answer obtained (carcinogenicity or non-carcinogenicity) is sometimes not clearcut. Finally, the test is time consuming and expensive. Nonetheless, because the bioassay remains the most definitive test for potential carcinogenicity, testing of chemicals which have been inadequately tested, and for which there is significant human exposure, will continue at a rate of 45 new starts.

There are two continuing objectives aimed at increasing the numbers of chemicals assessed for carcinogenicity and at increasing the breadth of information in the bioassay about the toxicology of a chemical. First, the NTP aims to develop and validate less expensive and more rapid methods that may set priorities for, or in some instances supplement the need for, long-term bioassays. An *in vivo* short-term test is described in this section, while studies on several *in vitro* test systems are described in the section on Cellular Toxicology. Second, the NTP seeks to broaden the experimental protocol for the bioassay, particularly during the prechronic phase, to include a number of special studies which will give more information on the general physiologic state of the animal as well as data on other toxicologic end points. It is hoped that such information will increase the utility of bioassay results in risk estimation.

FY 1980 Accomplishments

At the end of FY 1980, the National Toxicology Program had 234 compounds in various phases of the carcinogenesis bioassay process. Of these, 40 were new starts and are currently in prechronic studies (Table 7). This represents a reduction from 79 bioassay starts in FY 1979. During the year, 24 bioassays were completed and the reports of the findings peer reviewed (Table 8). Of these, final reports were issued for 15 with the remainder to be issued early in FY 1981. Under the conditions of the tests, 11 (45%) were considered negative, 12 (50%) positive, and 1 (5%) equivocal as to carcinogenicity. Thirty-four bioassays are currently in the histopathology-report sequence (Table 9). One hundred and eighty-one bioassays were in various phases of animal experimentation (Table 10).

A major accomplishment in the carcinogenesis testing program during FY 1980 was the expansion of the carcinogenic bioassays to broaden the understanding of the test chemical's toxic effects. Previously, the bioassay included prechronic studies only for establishment of appropriate doses in the chronic phase. The current toxicologic characterization includes a wide variety of additional special studies integrated into the prechronic experiments. To date, additional studies include clinical chemistry, hematology, urinalysis, pharmacokinetics, metabolism, immunotoxicology, neurobehavioral toxicology, and endocrinology. About two-thirds of the chemicals designated to begin bioassay in FY 1980 had one or more special studies included in their experimental design.

To perform the expanded toxicological characterization of chemicals, the NTP is using a contracting mechanism under which laboratories and their personnel are qualified for standard bioassays and in each of the various special study areas. During FY 1980, twenty-one facilities were found qualified in some or all other test procedures currently used by NTP. These institutions and the areas of expertise are listed in Table 11.

To better monitor the carcinogenesis testing program, especially with the inclusion of various special studies, the NTP determined that the program could be best performed through direct management and supervision of each chemical test. The process is described in the Chemical Management section on p. 97. Bioassays started in FY 1980 are under direct NTP management while testing activities initiated prior to FY 1980 will continue to proceed through the prime contract mechanism.

In conjunction with NTP initiation of direct arrangements with testing laboratories, a number of other scientific support contracts were advertised and competitively awarded in FY 1980. These include pathology support, health and safety activities, chemical repository, chemical analytical services, animal production, and literature searching.

Carcinogenicity testing traditionally begins with young animals (typically six-week-old rodents). However, human chemical exposures may include the periods of *in utero* development and infancy. The adequacy of standard chronic bioassay tests as contrasted with methods that include prenatal and neonatal exposures continues to be evaluated. Three chemicals are being evaluated in prechronic phases of the bioassay: a polybrominated biphenyl (PBB), phenytoin (diphenylhydantoin), and ethylene thiourea, using *in utero* and neonatal exposure.

Inhalation bioassays for carcinogenicity, like those by other routes, usually involve a two-year duration of exposure. Because the specialized facilities required for inhalation studies are expensive and commit scarce technical manpower for extended time periods, studies with mice, rats and hamsters were undertaken that used a design which varies the ages of animals exposed and the duration of inhalation exposure. Vinyl chloride, a known human carcinogen, was used. Preliminary analysis of the data after up to 12 months exposure in rats and hamsters confirmed that the duration of exposure and age at initiation of exposure are critical factors. In rats the most common tumor was hepatic angiosarcoma and in hamsters mammary gland carcinoma and hepatic angiosarcoma were the most frequent. Long-term studies by the inhalation route on the carcinogenic and general toxicologic effects of asbestos were in progress. The inhalation studies were designed to assess carcinogenic potential, fibrogenic properties, and lung clearance of three asbestos fiber types and one form of fiber glass. In concurrent studies with orally administered asbestos, preliminary results of lifetime oral studies in hamsters, and after 18 months in rats, suggest that none of the fiber types produced life shortening in exposed animals.

During FY 1980 there was continuation of a program to determine the applicability of the lung adenoma test in Strain A mice relative to findings in the two-year bioassay. One facility, the University of California at San Diego, is evaluating under code 66 chemicals that have completed bioassays. To validate the interlaboratory reproducibility of the

lung adenoma test, 34 of these chemicals, coded differently, are also under study at the Oak Ridge National Laboratory.

FY 1981 Program Plans

During FY 1981, the National Toxicology Program plans to start 45 carcinogenesis bioassays. Forty of these are listed in Table 12. This level is comparable to FY 1980. It is expected that 34 long-term bioassays will be completed and the draft reports of the results peer reviewed in FY 1981 (Table 9). All of the new animal bioassay starts during the year will include broadened protocols with various special studies integrated into the experimental design.

Also, during FY 1981, several long-term carcinogenesis studies, not formally included in the bioassay program, will be conducted. These investigations, both ongoing and new, will examine the carcinogenic properties of the following substances (routes): methyl ethyl ketone peroxide (inhalation); 1,2-dichloroethane (inhalation); 2-nitropropane (inhalation); foundry particulates (inhalation); dimethylformamide (inhalation); roofing asphalts (skin); machine oils (skin); and two azo dyes, acid black 52 and disperse yellow 3, (feeding). All studies use the standard bioassay protocol. However, some of the studies will not be two-year tests.

The NTP will continue to develop the Toxicology Data Management System (TDMS) as an automated data input system for carcinogenesis bioassays. The prototype hardware for the TDMS was delivered in late 1980. On-line testing of the modular system will begin in the first half of FY 1981.

Developmental and prechronic studies concerned with *in utero* and neonatal exposure of animals to carcinogens will be completed early in FY 1981. Standard bioassays with six-week-old animals will be initiated concurrently with bioassays where exposure begins *in utero* and continues during the neonatal period using a polybrominated biphenyl (PBB), phenytoin and ethlyene thiourea as the test chemicals. The objective is to determine whether extending long-term chemical exposure of animals to the gestational and neonatal periods will result in heightened or altered sensitivity to induction of carcinogenesis and/or other types of toxic effects.

Studies aimed at validating the applicability of the mouse lung adenoma test as a short-term *in vivo* carcinogenesis assay will continue during FY 1981. The results will also provide information on the interlaboratory reproducibility of the test.

Inhalation exposure studies with vinyl chloride in rodents which seek to deremine whether there is an optimal animal age and exposure window for such studies will be completed during the year. Several of the long-term studies on the toxicology of asbestos by inhalation and oral ingestion will be completed during FY 1981.

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TABLE 6

Phases of the Two-Year Carcinogenesis Bioassay

Phase I. Pretesting (15 months)

1. Development of Toxicology Information Package
2. Development of Bioassay Design
3. Development of Health and Safety Package
4. Purchases and Analysis of Chemical
5. Preparation of BID Packages in Groups of Chemicals
6. Selection of Bioassay Laboratory and Scheduling of Study Start

*Phase II. Initial Toxicology Characterization (11 months)

1. Acute Toxicology Tests
2. Subchronic Toxicology Tests
3. Receipt of Toxicology Characterization Report
4. Evaluation of Data and Setting of Final Experimental Design

Phase III. Chronic Bioassay (25 months)

1. Start of Chronic Test
2. Completion of Chronic Test

Phase IV. Summary Report Preparation by Laboratory (3 months)

1. Receipt of Materials and Methods Report
2. Receipt of Histopathologic Diagnoses to Data System
3. Receipt of Histopathology Report

Phase V. Internal Program Review (6 months)

1. Pathology Confirmation (Validation, Quality Assurance)
2. Data Evaluation, Initial (Determination of Adequacy of Bioassay)
3. Report Preparation and Statistical Analysis
4. Data Evaluation, Final (Program Review of Final Report)

Phase VI. External Program Review (2 months)

1. NTP Peer Review

Phase VII. Report Issuance (2 months)

1. Implementation of Program Review Modifications
2. Report Issuance

*A bioassay is ongoing and a chemical is "on test" from Phases II through VI (47 months, avg.) Phase I begins after a chemical is selected. Times given for each Phase are average times.

TABLE 7

CHEMICALS STARTING IN CARCINOGENESIS BIOASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	SPECIES *	ROUTE *	CAS NO.	NTP NO.
1	Allyl glycidyl ether	r,m	inhal	106-92-3	10824-H
2	Benzaldehyde	r,m	gav	100-52-7	10087-A
3	Butyrolactone	r,m	gav	96-48-0	10090-F
4	Catechol	r,m	gav	120-80-9	10094-W
5	Chloramine	r,m	water	10599-90-3	10313-V
6	Chloroacetophenone	r,m	inhal	532-27-4	10625-C
7	Dichlorvos	r,m	gav	62-73-7	10017-V
8	DMBA/TPA	r,m	sp	57-97-6	10371-J
9	Epinephrine hydrochloride	r,m	inhal	55-31-2	10041-V
10	Ethyl bromide	r,m	inhal	74-96-4	10067-J
11	Ethyl chloride	r,m	inhal	75-00-3	10019-D
12	Ethylene oxide	r,m	inhal	75-21-8	10020-A
13	Formaldehyde	m	inhal	50-00-0	10002-S
14	Furan	r,m	gav	110-00-9	10119-H
15	Furfural	r,m	gav	98-01-1	10120-F
16	Furfuryl alcohol	r,m	gav	98-00-0	10121-J
17	Hexachlorocyclopentadiene	r,m	gav	77-47-4	10125-A
18	Mercaptobenzothiazole	r,m	gav	149-30-4	10073-C
19	Methyl carbamate	r,m	gav	598-55-0	10642-F
20	Methylene chloride	r,m	inhal	75-09-2	10030-H
21	Nalidixic acid	r,m	feed	389-08-2	10045-K
22	Nitrofurantoin	r,m	feed	67-20-9	10382-W
23	P-Nitrophenol	m	sp	100-02-7	10142-E
24	P-Quinone	r,m	gav	106-51-4	10162-V
25	Pentachloroanisole	r,m	gav	1825-21-4	10024-R
26	Pentachloronitrobenzene	r,m	feed	82-68-8	10033-V
27	Pentachlorophenol	m	feed	87-86-5	10429-G
28	Pentaerythritol tetranitrate	r,m	feed	78-11-5	10150-E
29	Phenylbutazone	r,m	gav	50-33-9	10354-F
30	Propylene	r,m	inhal	115-07-1	10538-R

* r = rat, m = mouse, gav = gavage, inhal = inhalation, sp = skin painting

TABLE 7

CHEMICALS STARTING IN CARCINOGENESIS BIOASSAYS DURING FY 1980

SEQ. NO.	CHEMICAL	SPECIES *	ROUTE *	CAS NO.	NTP NO.
31	Roxarsone	r,m	feed	121-19-7	10233-F
32	Tetrachloroethylene	r,m	inhal	127-18-4	10176-T
33	Tetranitromethane	r,m	inhal	509-14-8	10025-V
34	Vinyl toluene	r,m	inhal	25013-15-4	10032-R
35	Wollastonite calcium silicates	r,h	it	13983-17-0	10027-D
36	1,2-Epoxybutane	r,m	inhal	106-88-7	10066-F
37	1,3-Butadiene	m	inhal	106-99-0	10514-J
38	2-Chlorobenzalmalononitrile	r,m	inhal	2698-41-1	10711-H
39	2,6-Xylidine	r,m	feed	87-62-7	10185-X
40	5-Hydroxytryptophan	r,m	gav	56-69-9	10128-L

* r = rat, m = mouse, h = hamster; inhal = inhalation, it = intratracheal, gav = gavage

TABLE 8

CHEMICALS FOR WHICH CARCINOGENESIS BIOASSAYS WERE COMPLETED IN FY 1980

SEQ. NO.	CHEMICAL	CARC ACTIVITY *	CAS NO.	NTP NO.	TR NO. **
1	Benzoin	N	119-53-9	10550-A	204
2	Bis(2-chloro-1-methylethyl) ether	N	108-60-1	10523-N	191
3	Butyl benzyl phthalate	P	85-68-7	10422-E	213
4	Caprolactam	N	105-60-2	10505-F	214
5	Cinnamyl anthranilate	P	87-29-6	10426-V	196
6	Cytembena	P	21739-91-3	10778-H	207
7	Di(2-ethylhexyl)adipate	N	103-23-1	10497-E	212
8	Dibromochloropropane	P	96-12-8	10465-X	206
9	Ethylene dibromide	P	106-93-4	10513-F	210
10	Fluometuron	S	2164-17-2	10697-P	195
11	Malathion	N	121-75-5	10563-V	192
12	Phenol	N	108-95-2	10076-N	203
13	Reserpine	P	50-55-5	10355-J	193
14	Selenium sulfide	P	7488-56-4	10745-X	194
15	Selenium sulfide	N	7488-56-4	10745-X	197
16	Selsun	N	SELSUN	10808-H	199
17	Sunset Yellow FCF 6	N	2783-94-0	10714-V	208
18	Toluene-2,6-diamine dihydrochloride	N	15481-70-6	10768-A	200
19	1,2,3,6,7,8(7,8,9)-Hexachlorodibenzo-p-dioxin (gavage)	P	HCDD MIX	10790-S	198
20	1,2,3,6,7,8(7,8,9)-Hexachlorodibenzo-p-dioxin (skin paint)	N	HCDD MIX	10790-S	202
21	2,3,7,8-Tetrachlorodibenzo-p-dioxin	P	1746-01-6	10157-G	209
22	2,3,7,8-Tetrachlorodibenzo-p-dioxin	P	1746-01-6	10157-G	201
23	4,4'-Methylenebis(N,N'-dimethylaniline)	P	101-61-1	10487-W	186
24	4,4'-Oxydianiline	P	101-80-4	10490-C	205

* CARCINOGENIC ACTIVITY: N = negative, P = positive, S = suspect

** NTP/NCI Technical Report Number

TABLE 9

CHEMICALS FOR WHICH CARCINOGENESIS BIOASSAYS WILL BE COMPLETED IN FY 1981

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
1	Agar agar	9002-18-0	10754-C	R,M	F
2	Allyl isothiocyanate	57-06-7	10367-A	R,M	G
3	Asbestos, amosite	12172-73-5	10761-X	H	F
4	Asbestos, chrysotile	12001-29-5	10758-S	H	F
5	Bis(2-chloro-1-methylethyl) ether	108-60-1	10523-N	M	G
6	Bisphenol A	80-05-7	10034-Y	R,M	F
7	D & C Red 9	5160-02-1	10729-X	R,M	F
8	Di(2-ethylhexyl) phthalate	117-81-7	10188-J	R,M	F
9	Disperse Yellow 3	2832-40-8	10716-D	R,M	F
10	Eugenol	97-53-0	10468-J	R,M	F
11	Gum arabic	9000-01-5	10751-P	R,M	F
12	Gum guar	9000-30-0	10752-T	R,M	F
13	Gum tara	39300-88-4	10795-E	R,M	F
14	Locust bean gum	9000-40-2	10753-X	R,M	F
15	Mannitol	69-65-8	10386-L	R,M	F
16	Melamine	108-78-1	10525-W	R,M	F
17	Methylenedianiline dihydrochloride	13552-44-8	10862-G	R,M	W
18	Mirex	2385-85-5	10699-X	R	F
19	N-Nitrosodiethanolamine	1116-54-7	10143-H	R,M	W
20	Orange 10	1936-15-8	10693-Y	R,M	F
21	Pentachloroethane	76-01-7	10149-G	R,M	G
22	Polybrominated biphenyls (Firemaster FF 1)	67774-32-7	10800-C	R,M	F
23	Propyl gallate	121-79-9	10564-Y	R,M	F
24	Red 14	3567-69-9	10723-Y	R,M	F
25	Stannous chloride	7772-99-8	10747-F	R,M	F
26	Yellow 14	842-07-9	10662-N	R,M	F
27	Zearalenone	17924-92-4	10770-C	R,M	F
28	Ziram	137-30-4	10590-S	R,M	F
29	1,1-Dichloroethylene	75-35-4	10109-A	R,M	G
30	1,1,1,2-Tetrachloroethane	630-20-6	10651-J	R,M	G

* SP = species, RT = route, R = rat, M = mouse, H = hamster, F = feed, G = gavage, W = water.

TABLE 9

CHEMICALS FOR WHICH CARCINOGENESIS BIOASSAYS WILL BE COMPLETED IN FY 1981

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
31	1,3-Dichloropropene	542-75-6	10560-H	R,M	G
32	1,4-Diamino-2,6-dichlorobenzene	609-20-1	10647-A	R,M	F
33	11-Aminoundecanoic acid	2432-99-7	10783-W	R,M	F
34	2-Biphenylamine	90-41-5	10438-K	R,M	F

* SP = species, RT = route, R = rat, M = mouse, G = gavage, F = feed.

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
1	Acid Orange 3	6373-74-6	10737-X	RM	G
2	Agaritine	2757-90-6	10713-R	RM	W
3	Allyl glycidyl ether	106-92-3	10824-H	RM	I
4	Allyl isovalerate	2835-39-4	10717-G	RM	G
5	Alpha-Methylbenzyl alcohol	98-85-1	10473-X	RM	G
6	Ampicillin	69-53-4	10010-S	RM	G
7	Antimony oxide	1309-64-4	10676-V	RM	F
8	Asbestos, amosite	12172-73-5	10761-X	R	F
9	Asbestos, chrysotile	12001-29-5	10758-S	R	F
10	Asbestos, crocidolite	12001-28-4	10757-H	R	F
11	Ascorbic acid	50-81-7	10357-S	RM	F
12	Benzaldehyde	100-52-7	10687-A	RM	G
13	Benzene	71-43-2	10389-Y	RM	G
14	Benzofuran	271-89-6	10058-F	RM	G
15	Benzyl acetate	140-11-4	10591-K	RM	G
16	Benzyl alcohol	100-51-6	10059-J	RM	G
17	Benzyl chloride	100-44-7	10481-X	RM	G
18	Blue 15B	574-93-6	10635-J	RM	F
19	Boric acid	10043-35-3	10035-B	M	F
20	Bromobenzene	108-86-1	10060-G	RM	G
21	Bromodichloromethane	75-27-4	10397-Y	RM	G
22	Bromoform	75-25-2	10396-V	RM	G
23	Butyrolactone	96-48-0	10090-F	RM	G
24	Castor oil	8001-79-4	10748-J	RM	F
25	Catechol	120-80-9	10094-M	RM	G
26	Chloramine	10599-90-3	10313-V	RM	W
27	Chlorendic acid	115-28-6	10028-G	RM	F
28	Chlorinated trisodium phosphate	56802-99-4	10061-K	RM	G
29	Chloroacetophenone	532-27-4	10625-C	RM	I
30	Chlorobenzene	108-90-7	10528-H	RM	G

* SP = species, RT = route, R = rat, M = mouse, G= gavage, W = water, I = inhalation, F = feed.

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
31	Chlorodibromomethane	124-48-1	10570-R	RM	G
32	Chlorowax 40	63449-39-8	10062-P	RM	G
33	Chlorowax 500C	63449-39-8	10063-T	RM	G
34	Chlorpheniramine maleate	113-92-8	10537-L	RM	G
35	Coconut diethanolamide	68603-42-9	10802-J	RM	SP
36	Cyclohexanone	108-94-1	10064-X	RM	W
37	D-Limonene	5989-27-5	10071-T	RM	G
38	Decabromodiphenyl oxide	1163-19-5	10672-E	RM	F
39	Diallyl phthalate	131-17-9	10578-X	RM	G
40	Dichlorvos	62-73-7	10017-V	RM	G
41	Diesel fuel marine	DIESEL FUEL	10805-W	RM	G
42	Diesel fuel marine	DIESEL FUEL	10805-W	M	SP
43	Diethanolamine	111-42-2	10534-A	RM	W
44	Diglycidyl resorcinol ether	101-90-6	10492-J	RM	G
45	Dimethyl hydrogenphosphite	868-85-9	10663-A	RM	G
46	Dimethyl methylphosphonate	756-79-6	10660-N	RM	G
47	Dimethyl morpholinophosphonate	597-25-1	10641-C	RM	G
48	Dimethylvinyl chloride	513-37-1	10623-T	RM	G
49	Diphenhydramine hydrochloride	147-24-0	10040-R	RM	F
50	Disperse Blue 1	2475-45-8	10707-Y	RM	F
51	Dodecyl alcohol, ethoxylated	9002-92-0	10755-F	RM	F
52	DMBA/TPA	57-97-6	10371-J	RM	SP
53	DMBA/TPA	57-97-6	10371-J	M	SP
54	Ephedrine sulfate	134-72-5	10584-P	RM	F
55	Epinephrine hydrochloride	55-31-2	10041-V	RM	I
56	Erythromycin stearate	643-22-1	10656-E	RM	F
57	Ethyl acrylate	140-88-5	10594-X	RM	G
58	Ethyl bromide	74-96-4	10067-J	RM	I
59	Ethyl chloride	75-00-3	10019-D	RM	I
60	Ethylene chlorohydrin	107-07-3	10517-W	RM	SP
61	Ethylene oxide	75-21-8	10020-A	M	I

* SP = species, RT = route, R = rat, M = mouse, G = gavage, SP = skin painting, W = water, F = feed, I = inhalation.

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
62	Fluorescein, sodium	518-47-8	10624-X	RM	W
63	Formaldehyde	50-00-0	10002-S	M	I
64	Furan	110-00-9	10119-H	RM	G
65	Furfural	98-01-1	10120-F	RM	G
66	Furfuryl alcohol	98-00-0	10121-J	RM	G
67	Furosemide	54-31-9	10068-N	RM	F
68	Geranyl acetate	105-87-3	10507-N	RM	G
69	Gibberellic acid	77-06-5	10407-H	RM	F
70	Gilsonite	12002-43-6	10760-T	RM	F
71	Glutaraldehyde	111-30-8	10003-W	RM	SP
72	Glycidol	556-52-5	10630-P	RM	G
73	Hematoxylin	517-28-2	10044-G	RM	F
74	Hexachlorocyclopentadiene	77-47-4	10125-A	RM	G
75	Hexylresorcinol	136-77-6	10588-F	RM	G
76	Hydrochlorothiazide	58-93-5	10029-K	RM	F
77	Hydroquinone	123-31-9	10022-H	RM	G
78	HC Blue 1	2784-94-3	10715-Y	RM	F
79	HC Blue 2	33229-34-4	10788-R	RM	F
80	HC Red 3	2871-01-4	10710-K	RM	G
81	Iodinated glycerol	5634-39-9	10733-G	RM	G
82	Isophorone	78-59-1	10070-P	RM	G
83	Lauric acid diethanolamine	7487-79-8	10744-T	RM	SP
84	Maleic hydrazide diethanolamine	5716-15-4	10734-K	RM	W
85	Malonaldehyde	542-78-9	10627-J	RM	G
86	Mercaptobenzothiazole	149-30-4	10073-C	RM	G
87	Methyl carbamate	598-55-0	10642-F	RM	G
88	Methyl methacrylate	80-62-6	10410-V	RM	I
89	Methyldopa	555-30-6	10629-S	RM	F
90	Methylene chloride	75-09-2	10030-H	RM	G
91	Methylene chloride	75-09-2	10030-H	RM	I
92	Monuron	150-68-5	10600-R	RM	F

* SP = species, RT = route, R = rat, M = mouse, W = water, I = inhalation, G = gavage, F = feed, SP = skin painting

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
93	N-Butyl chloride	109-69-3	10089-H	RM	G
94	N-Phenyl-2-naphthylamine	135-88-6	10586-X	RM	F
95	N,N-Dimethylaniline	121-69-7	10039-T	RM	G
96	Nalidixic acid	389-08-2	10045-K	RM	F
97	Naphthalene	91-20-3	10046-P	RM	G
98	Navy fuels JP-5	NAVY FUELS	10140-W	M	SP
99	Navy fuels JP-5	NAVY FUELS	10140-W	R	G
100	Nitrofurantoin	67-20-9	10382-W	RM	F
101	Nitrofurazone	59-87-0	10047-T	RM	F
102	O-Phenylphenol	90-43-7	10439-P	M	SP
103	Oleic acid diethanolamine	13961-86-9	10764-J	RM	SP
104	Oxalic acid	144-62-7	10049-C	RM	F
105	Oxytetracycline hydrochloride	2058-46-0	10080-X	RM	F
106	P-Nitrophenol	100-02-7	10142-E	M	SP
107	P-Quinone	106-51-4	10162-V	RM	G
108	P-Rosaniline hydrochloride	569-61-9	10633-C	RM	F
109	Penicillin VK	132-98-9	10581-U	RM	G
110	Pentachloroanisole	1825-21-4	10024-R	RM	G
111	Pentachloronitrobenzene	82-68-8	10033-V	M	F
112	Pentachlorophenol, purified	87-86-5	10429-G	M	F
113	Pentachlorophenol, Technical grade	87-86-5	10429-G	M	F
114	Pentachlorophenol, Dowicide EC-7	87-86-5	10429-G	M	F
115	Pentachlorophenol, DR-2	87-86-5	10429-G	M	F
116	Pentaerythritol tetranitrate	78-11-5	10150-E	M	F
117	Phenolphthalein	77-09-8	10050-Y	RM	F
118	Phenylbutazone	50-33-9	10354-F	RM	F
119	Phenylephrine hydrochloride	61-76-7	10376-E	RM	F
120	Phthalocyanine green	1328-53-6	10680-E	RM	F
121	Propylene	115-07-1	10536-R	RM	I
122	Pyridine	110-86-1	10532-S	RM	G
123	Rhodamine 6G	989-38-8	10052-G	RM	F

* SP = species, RT = route, R = rat, M = mouse, G = gavage, F = feed, SP = skin painting, I = inhalation

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
124	Rotenone	83-79-4	10420-W	RM	F
125	Roxarsone	121-19-7	10233-F	RM	F
126	Sodium (2-ethylhexyl)alcohol sulfate	126-92-1	10572-Y	RM	F
127	Sodium aluminosilicate	1344-00-9	10054-P	RM	F
128	Sodium cyanurate	2624-17-1	10710-E	RM	G
129	Sodium dodecyl sulfate	151-21-3	10604-G	RM	F
130	Sodium fluoride	7681-49-4	10746-C	RM	W
131	Sodium xylenesulfonate	1300-72-7	10184-T	RM	F
132	Styrene oxide	96-09-3	10464-T	RM	G
133	Succinic anhydride	108-30-5	10518-A	RM	G
134	Tert-Butyl alcohol	75-65-0	10402-N	RM	W
135	Tetrachloroethylene, B	127-18-4	10176-T	RM	G
136	Tetrachloroethylene, C	127-18-4	10176-T	R	G
137	Tetrachloroethylene, D	127-18-4	10176-T	R	G
138	Tetrachloroethylene, E	127-18-4	10176-T	R	G
139	Tetrachloroethylene, F	127-18-4	10176-T	RM	I
140	Tetracycline hydrochloride	64-75-5	10381-S	RM	F
141	Tetrakis(hydroxymethyl)phosphonium chloride	124-64-1	10171-Y	RM	G
142	Tetranitromethane	509-14-8	10025-V	RM	I
143	Toluene diisocyanate	584-84-9	10638-W	RM	G
144	Tremolite	14567-73-8	10766-S	R	F
145	Trichlorfon	52-68-6	10360-X	RM	G
146	Trichloroethylene, B	79-01-6	10175-P	RM	G
147	Trichloroethylene, C	79-01-6	10175-P	R	G
148	Trichloroethylene, D	79-01-6	10175-P	R	G
149	Trichloroethylene, E	79-01-6	10175-P	RM	G
150	Trichloroethylene, F	79-01-6	10175-P	R	G
151	Tris(2-ethylhexyl) phosphate	78-42-2	10413-A	RM	G
152	THPS	55566-30-8	10809-L	RM	G
153	Vinyl toluene	25013-15-4	10032-R	RM	I
154	Witch hazel	68916-39-2	10183-P	RM	SP

* SP = species, RT = route, R = rat, M = mouse, F = feed, G = gavage, W = water, I = inhalation, SP = skin painting

TABLE 10

CHEMICALS IN TESTING PHASES OF THE CARCINOGENESIS BIOASSAY DURING FY 1980

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
155	Wollastonite calcium silicates	13983-17-0	10027-D	RH	IT
156	Xylenes, commercial mixture	1330-20-7	10004-A	RM	G
157	1,1,1-Trichloroethane	71-55-6	10390-W	RM	G
158	1,2-Dichlorobenzene	95-50-1	10456-T	RM	G
159	1,2-Dichloropropane	78-87-5	10111-C	RM	G
160	1,2-Epoxybutane	106-88-7	10066-F	RM	I
161	1,2-Epoxyhexadecane	7320-37-8	10740-D	RM	SP
162	1,2-Epoxypropane	75-56-9	10400-F	RM	I
163	1,3-Butadiene	106-99-0	10514-J	M	I
164	1,4-Dichlorobenzene	106-46-7	10038-P	RM	G
165	2-Amino-4-nitrophenol	99-57-0	10005-E	RM	G
166	2-Amino-5-nitrophenol	121-88-0	10565-D	RM	G
167	2-Butanone peroxide	1338-23-4	10001-N	RM	SP
168	2-Chlorobenzalmalononitrile	2698-41-1	10711-H	RM	I
169	2-Ethoxyethanol	110-80-5	10117-A	RM	G
170	2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	10722-V	RM	G
171	2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	10722-V	M	SP
172	2,3-Dibromo-1-propanol	96-13-9	10016-R	RM	G
173	2,3-Dibromo-1-propanol	96-13-9	10016-R	M	SP
174	2,4-Dichlorophenol	120-83-2	10557-D	RM	F
175	2,6-Xylidine	87-62-7	10185-X	RM	F
176	3-Chloro-2-methylpropene	563-47-3	10632-X	RM	G
177	4-Vinylcyclohexene	100-40-3	10480-T	RM	G
178	4,4'-Diphenylmethane diisocyanate	101-68-8	10488-A	RM	G
179	5-Hydroxytryptophan	56-69-9	10128-L	RM	G
180	8-Hydroxyquinoline	148-24-3	10598-N	RM	F
181	8-Methoxypsoralen	298-81-7	10023-L	R	G

* SP = species, RT = route, R = rat, H = hamster, M = mouse, IT = intratracheal, G = gavage, I = inhalation, SP = skin painting, F = feed.

TABLE 11

LABORATORIES QUALIFIED FOR CARCINOGENESIS BIOASSAYS AND VARIOUS SPECIAL STUDIES

NCI/BOA	[a]Routes of Administration					Special Capabilities				
	DF	DW	GV	SP	III	Clinical Chemistry	Pharmacokinetics Metabolism	Immuno-Toxicology	Neurobehavioral Toxicology	Endocrinology
Battelle-Columbus	X	X	X	X		Yes	Yes	Yes		
Battelle-MW	X	X	X	X	X	Yes	Yes	Yes	Yes	
Bioassay Systems		X	X	X		Yes				
[e]Eppley	X	X	X	X			Yes			
[e]FDRL	X	X	X	X		Yes				
[e]GSRI	X	X	X	X						
Hazleton	X	X	X	X	X	Yes		Yes		Yes
[e]IITRI TASK I only[d]	X	X	X	X	X			Yes		
[e]IRDC	X	X	X	X	X	Yes				
Inveresk	X	X	X	X	X	Yes	Yes[c]		Yes	
Litton Bionetics	X	X	X	X	X	Yes		Yes		Yes
Mason	X	X	X	X		Yes		Yes		
Microbiological Assoc.	X	X	X	X				Yes		
Midwest Res. Inst.	X	X	X	X	X	Yes	Yes			
Oregon State TASK I only		X	X	X				Yes		
Papanicolaou	X	X	X	X						
Raltech	X	X	X	X	X[b]	Yes				
Southern Res. Inst.	X	X	X	X		Yes	Yes			
Springborn	X	X	X	X						
Stanford Res. Inst.	X	X	X	X		Yes	Yes	Yes	Yes	
Texas A&M TASK I only	X	X	X	X		Yes				
Totals	19	21	21	21	8	14	8	9	3	2

[a]Dosed-feed, drinking water, gavage, skin paint, inhalation.

[b]Acute and 14 day repeated-dose only

[c]Restricted to Shady Grove animal facility

[d]Task I is prechronic studies

[e]FDRL (Food and Drug Research Laboratories, Inc.)
GSRI (Gulf South Research Institute)
IITRI (Illinois Institute of Technology Research Institute)
IRDC (International Research and Development Corporation)

TABLE 12

CHEMICALS SCHEDULED TO START CARCINOGENESIS BIOASSAYS IN FY 1981

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
1	Amphetamine sulfate	60-13-9	10085-S	RM	F
2	Azodicarbonamide	123-77-3	10086-M	RM	F
3	Beta-Cadinene	523-47-7	10091-J	RM	F
4	C I Pigment Red 23	6471-49-4	10210-D	RM	F
5	C I Pigment Red 3	2425-85-6	10209-F	RM	F
6	Carvone	99-49-0	10093-S	RM	F
7	Chloramphenicol	56-75-7	10096-E	RM	F
8	Chlorpromazine hydrochloride	69-09-0	10101-T	RM	F
9	Curcumin	458-37-7	10105-J	RM	F
10	Diethyl phthalate	84-66-2	10112-F	RM	F
11	Dimethoxane	828-00-2	10114-N	RM	G,SP
12	Dimethyloldihydroxyethyleneurea	1854-26-8	10205-P	RM	G,I
13	Ethylene glycol	107-21-1	10118-E	RM	F
14	Ethylenediamine	107-15-3	10190-K	RM	G
15	Glycol (Polysorbate 80)	9005-65-6	10122-N	RM	F
16	Hexachloroethane	67-72-1	10126-E	R	G
17	HC Yellow 4	52551-67-4	10123-S	RM	F
18	Isobutyl nitrite	542-56-3	10869-J	RM	I
19	Isoproterenol hydrochloride	51-30-9	10130-N	RM	I
20	Mercuric chloride	7487-94-7	10133-A	RM	F
21	Methyl coumarin	92-48-8	10136-L	RM	G
22	Monochloroacetic acid	79-11-8	10138-V	RM	G
23	N-Methylolacrylamide	924-42-5	10206-T	RM	F
24	Nitrobenzene	98-95-3	10141-A	RM	G,SP
25	Ochratoxin A	37203-43-3	10268-Y	RM	G
26	P-Chloroaniline	106-47-8	10100-P	RM	F
27	Palladium chloride (2+)	7647-10-1	10148-D	RM	F
28	Probenecid	57-66-9	10160-L	RM	F
29	Quercetin	117-39-5	10161-R	RM	F
30	Resorcinol	108-46-3	10163-Y	RM	G

* SP = species, RT = route, R = rat, M = mouse, F = feed, G = gavage, SP = skin paint, I = inhalation

TABLE 12

CHEMICALS SCHEDULED TO START CARCINOGENESIS BIOASSAYS IN FY 1981

SEQ. NO.	CHEMICAL	CAS NO.	NTP NO.	SP*	RT*
31	Sodium azide	26628-22-8	10164-D	RM	G
32	Titanium ferrocene	1271-19-8	10174-K	RM	G
33	Toluene	108-88-3	10009-V	RM	G,I
34	Tris(2-chloroethyl) phosphate	115-96-8	10178-C	RM	F
35	Vinyl cyclohexene dioxide	106-87-6	10179-F	RM	G,SP
36	1-Amino-2,4-dibromoanthraquinone	81-49-2	10004-N	RM	F
37	2,4-Diaminophenol dihydrochloride	137-09-7	10106-N	RM	F
38	3,4-Dihydrocoumarin	119-84-6	10113-J	RM	G
39	4-Hydroxyacetanilide	103-90-2	10127-H	RM	F
40	4,4'-Diamino-2,2'-stilbenedisulfonic acid	81-11-8	10107-S	RM	F

* SP = species, RT = route, R = rat, M = mouse, G = gavage, I = inhalation, F = feed, SP = skin painting.

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General Toxicology

Most chemicals selected for testing by NTP are chosen because the potential exists for considerable human exposure, and too little is known about their toxicologic effects. The scope of toxic action of an environmental agent is exercised on the entire organism. Within that organism, one seeks to identify a target organ or organs in which toxic injury produces dysfunction or overt disease. The general toxicology program uses a toxicologic screen to gather information on generalized toxicity of chemicals to test animals. Second, the program seeks to include tests which will give presumptive evidence of specific chemically induced damage to vital organs, such as lungs, liver and kidneys; fertility and reproduction; the nervous system and behavior; and the immune system. The screen also establishes the range of doses over which various toxicities occur, toxicological variability between males and females in two species of animals, and in some instances establishes the basic disposition pattern of a chemical within the body as a function of dose and time.

The general toxicology rodent screen is a major component of Phase I testing (Table 2). These Phase I tests should result in a core of toxicology data essential to the proper design of more extensive studies. Using the information from the Phase I rodent toxicologic screen, more extensive toxicologic testing can be started with increased capabilities to confirm and define those toxicities identified in the screen.

FY 1980 Accomplishments

Acute, subchronic and chronic studies aimed at characterizing the toxicologic potential of several chemicals of interest to the NTP were continued or begun in FY 1980. Chronic toxicology studies with a polybrominated biphenyl (PBB) mixture and its major component, a hexabromobiphenyl, were in progress during FY 1980. Subchronic toxicology studies were carried out with chlordecone (Kepone) and were aimed at examining general toxic effects and chemical disposition, as well as effects on fertility and reproduction and neurobehavioral function. Among effects seen were dose-related decreased fertility in male rats, and behavioral effects in males and females.

In test method development, particular emphasis was given to evaluating the sensitivity of a number of tests of renal function using subchronic exposure of Fischer rats to three different types of renal toxicants. It was found that the most promising types of renal function tests were those that measured total functional capacity of the kidneys. Many standard renal function tests were found to be of little value in detecting kidney injury. Further, direct linear measurement of urinary protein using an automated centrifugal analyzer proved to be sensitive, accurate and precise in rodent studies.

Development of expanded protocals for 90-day subchronic tests was a significant activity. Tests were selected to be added to prechronic studies in the areas of clinical chemistry, liver function, kidney function, thyroid function, urinalysis, sperm function, as well as specific screens or organ functions and damage. Some of these tests have been included in the prechronic phase of the two-year carcinogenesis bioassay.

FY 1981 Program Plans

The developmental effects of chlordecone (Kepone) will be assessed in rats. Effects on neurobehavioral development and on reproduction and fertility also will continue to be examined. Indepth studies will continue on the renal toxicology of 1,2-dibromo-3-chloropropane (DBCP), haloalkanes and several commercial solvents. Other selected chemicals will be studied for various toxic effects using expanded protocols.

The evaluation of tests for detecting kidney injury in subacute, subchronic and chronic toxicity studies will be expanded to include additional test procedures (e.g., electrophoretic separation of urinary proteins) and other classes of toxicants. Procedures using urine will be emphasized since these are noninvasive. The development and adaptation of test procedures for automated analyses will be continued.

The area of cutaneous toxicology will receive emphasis, primarily in development and evaluation of methods to measure toxicity of chemicals to skin, especially solvents.

During FY 1981, development of exanded protocals will continue, primarily for use in the general toxicologic rodent screen, and in the prechronic phase of the carcinogenesis two-year bioassay. Attention will be given both to increasing the types of toxic effects that can be measured and to improving or replacing currently employed assays. Expansion of the systemic pathologic examination at the high dose level in 90-day studies will continue. Development of exanded and improved protocols reflect the NTP's ongoing commitment to broadening toxicologic characterization of chemicals tested, and development and validation of improved protocols to better meet regulatory needs.

Chemical Disposition

Knowledge of the disposition, i.e. absorption, distribution, metabolism and excretion, of chemicals to which animals are exposed is fundamental to an understanding of the mechanisms by which exposure to chemicals induces toxicity. The objective of the Chemical Disposition program is to assist in interpreting and using available information on the disposition of chemicals and in developing new basic knowledge where needed. This data will help to more accurately predict the correct doses for compounds to be studied in animal bioassays. Developing fundamental information on chemical structure-activity relationships will permit a more accurate prediction of the disposition of large classes of chemicals and of chemicals of unrelated classes but which have similar structural or physical properties. The ultimate goal of the Chemical Disposition program is to provide basic data which will permit a more accurate extrapolation of laboratory data to humans.

Chemical disposition studies are designed to determine the absorption, degree of metabolism and rate of clearance of the compound of choice in one or more animal species at a low and a high dose administered via the anticipated route of human exposure, usually oral. The low dose is determined by the limits of accurate detection or the anticipated human exposure, whichever is higher. The high dose is determined by the lower limits of acute toxicity or the highest dose which can be accurately administered, whichever is lower. If absorption, metabolism and clearance are apparently unaffected by dose, the disposition of the chemical is studied at a relatively non-toxic dose which usually does not exceed anticipated human exposure by greater than 10-fold. If either absorption, metabolism or clearance is affected by dose, the initial studies are repeated with intermediate doses in order to determine the saturating dose for the biological mechanism involved.

FY 1980 Accomplishments

The chemical disposition effort in FY 1980 was conducted principally through two university-based contracts and a small in-house program staffed by three scientists plus technical support. Current program capacity is 10–15 chemical disposition starts yearly.

For the most efficient use of this limited capacity, preference is given to development of a core of knowledge based on chemical class characteristics

that can be used to predict the disposition of other chemicals within that class of in related classes. Studies on four major chemical classes were initiated or continued under NTP in FY 1980: aromatic and aliphatic amines, benzidine-based dyes, haloalkyl phosphates and halogenated polyaromatics.

Benzidine and seven benzidine-based dyes were studied in the dog and the rat. Dogs excreted free benzidine in the urine following oral administration of the dyes in amounts comparable to the benzidine excreted in urine following a similar dose of pure benzidine. Rats did not excrete benzidine in the urine following *acute* administration of the benzidine-based dyes, but did excrete benzidine and N-acetyl benzidine following chronic administration of several benzidine-based dyes.

Two 3,3'-dimethoxybenzidine-based dyes and four 3,3,'-dimethylbenzidine-based dyes were studied in dogs and rats. Both dogs and rats excreted free dimethoxybenzidine in the urine following oral administration of the dimethoxybenzidine-based dyes. Both species excreted unchanged 3,3,'-dimethylbenzidine in urine following the oral administration of two of the dimethylbenzidine-based dyes, direct Blue 25 and Acid Red 114.

The metabolisms of two polychlorinated biphenyls (PCBs) that are readily metabolized and one that is resistant to metabolism were studied *in vitro* and *in vivo* in three species—rat, dog and monkey. The results of the studies indicated that at least in some cases it may be possible to predict *in vivo* metabolism and disposition of chemicals based on rates of *in vitro* metabolism.

Studies with 2,3,7,8,-tetrachlorodibenzofuran (TCDF) showed that it is readily absorbed from the gastrointestinal tracts of rats and guinea pigs, and absorption is unaffected by the size of the dose within the dose range studied. Following either oral or intravenous administration, TCDF is initially concentrated in the livers of rats, guinea pigs and monkeys. The rat metabolizes TCDF at an appreciable rate and excretes the metabolites in the bile and ultimately in the feces. The guinea pig, apparently unable to metabolize TCDF, stores it for an extended period of time and is very sensitive to intoxication by TCDF. In multiple dose experiments with guinea pigs, symptoms of acute intoxication are observed only after a critical body burden is accumulated. The monkey metabolizes and excretes TCDF at a rate which is intermediate between that of the rat and guinea pig. Current effort is directed toward isolation and identification of a metabolite from monkey feces.

Studies of a uniquely toxic PCB, 3,4,3',4'-tetrachlorobiphenyl (TCB), in male and female rats and female monkeys have shown this PCB to be metabolized and excreted at a rate which is intermediate between that of rapidly metabolized and persistent PCBs which have been the subjects of past studies. No appreciable sex-related difference was observed in the disposition of TCB in rats. A species-related difference was observed for the disposition of TCB in a comparison of rats and monkeys. The biological half-life of TCB in the monkey was approximately five times that observed for the rat. The major difference in metabolism observed for TCB as opposed to other less toxic PCBs is that a metabolite of TCB persists in the blood longer than any other PCB or PCB metabolite so far studied.

The findings described here and in previous years provide a basis for the following conclusions about simple halogenated aromatics: (a) their lipid solubility facilitates absorption; (b) their half-lives are determined by the rate at which they are metabolized; (c) their ability to be metaolized is determined by the position, as well as the degree of halogenation; and (d) the major sites of accumulation are the liver, skin and adipose tissue and the relative importance of the liver and adipose tissues as storage sites is determined by the polarity of the compound in question.

The metabolism and disposition of two halogenated alkyl phosphates, tris (1,3-dichloro-2-propyl) phosphate (Fyrol FR–2) and tris (2,3-dibromopropyl) phosphate (Tris), were studied in the rat. The major mechanisms of metabolism involve dealkylations of the phosphate. The dealkylated products undergo various degrees of further metabolism and may be metabolized all the way to CO_2. *In vitro* studies have demonstrated that the dealkylations are mediated by both mixed-function oxidase enzymes and a soluble glutathione-S-transferase enzyme. Trace amounts of each of these compounds are metabolized to reactive intermediates which alkylate subcellular macromolecules. The major differences relating to chemical structure are observed in the alkylation of DNA in the kidney where treatment with Tris results in approximately 10-fold greater DNA alkylation than does a similar Fyrol FR–2 treatment.

Other studies were initiated during FY 1980 on the metabolism and disposition of chlorpheniramine maleate, acrylamide, p-chloroaniline and p-nitrotoluene.

FY 1981 Program Plans

A continuing objective of the chemical disposition program is to incorporate chemical disposition information into the beginning of the long-term bioassay process to assist chemical managers in dose selection and other decisions relating to the long-term testing of a chemical. A second objective is to design and conduct experiments which will enable relating chemical disposition and kinetic data to what one might expect to see in humans.

The NTP plans to award two new contracts which will increase the capacity of the program to 20–25 chemical starts a year by the end of FY 1981. Plans for FY 1981 call for the continuation of ongoing studies in chemical disposition, and initiation of 12 additional studies of compounds or classes of compounds.

Studies on the chemical disposition of benzidine-based dyes will continue. Current plans call for the use of radiolabeled compounds to accurately quantitate gastrointestinal absorption, distribution, metabolism and excretion of benzidine, 3,3'-dimethylbenzidine and 3,3'-dimethoxybenzidine. Radiolabeled benzidine will also be used to synthesize a radiolabeled benzidine-based dye to be used in similar studies of absorption, distribution, metabolism and excretion. The data from these studies will be used to calculate the kinetic parameters for the disposition of these compounds, and an effort will be made to extrapolate this data to the human condition in order to assess the hazard posed from human exposure to dyes synthesized from these carcinogenic precursors.

The work on comparing *in vitro* vs. *in vivo* metabolism of PCBs will be continued to refine the technique and hopefully provide data which will permit the extrapolation of these results to man.

Halogenated foreign chemicals are the most toxic and persistent of the chemicals contaminating our environment. Studies done to date have firmly established those factors which determine the disposition of simple halogenated aromatics. Future studies will be designed to expand this base of knowledge by determining how other types of substitution, in addition to halogens, affect the metabolism and disposition of organic compounds. In addition, the effort to elucidate the biochemical mechanism(s) by which halogenated hydrocarbons exert their action will be continued.

Data from the studies of chlorpheniramine maleate, acrylamide, p-chloroaniline and p-nitrotoluene, a series of aliphatic and aromatic amines plus p-nitrotoluene, which may be metabolically reduced to an amine, will be further analyzed in an effort to determine the effect of the amine group on the disposition of these compounds.

Immunological Toxicology

The functions of the immune system are host defense, maintenance of homeostasis and surveillance. Stimuli can be either endogenous of exogenous and the immune response either specific or nonspecific. The interactions of environmental chemicals of drugs with the immune system may result in undersirable effect of three types: (1) those determined by immunodeficiency or immune suppression, (2) those determined by alterations of host defense mechanisms, and (3) those determined by allergy or hypersensitivity. Although the system is remarkably resilient, drugs, chemicals, ionizing radiation and malnutrition can impair its function. There is increasing evidence that chronic, subclinical exposure to certain chemicals may depress immune responsiveness and increase susceptiblility to infectious agents.

The primary objective of the program in immunological toxicology is to develop and validate a series of ummunologic procedures to define a relatively simply screening battery of tests for implementation in the NTP chemical testing programs. Chemical suspected of causing immunologic alterations will be examined to aid in validation of the screening battery.

Early in FY 1980, a consensus meeting on immunotoxicology was held at NIEHS brining together over 35 immunologists, pathologists and toxicologists to develop a list of relevant immunological parameters for evaluation of chemical toxicity. There was general agreement that the discipline of immunology provide sensitive assay procedures to examine selective and general cellular toxicology since the immune system is composed of a variety of easily characterized functional subsets of rapidly proliferating cells.

The consensus group endorsed the development and validation of a comprehensive panel of assays including: (1) host resistance to bacterial and tumor cell challenge; (2) cell-mediated immune function as measures by lymphoproliferative responses to mitogens; (3) development of delayed hypersensitivity to T-cell dependent antigen; (4) assessment of antibody plaque forming cell responses; (5) quantitation of immunoglobulin levles; and (6) bone marrow progenitor cell assays.

FY 1980 Accomplishements

During FY 1980 several chemicals were examined for immunotoxic effects using a comprenhensive panel of immunology and host resisteance assays. Routine clinical chemistry, hematology and pathology/histology studies were also performed. All the chemicals were examined at three dose levels which were not believed to be overtly toxic in terms of causing negative weight gain or gross changes in liver pathology or chemistry. Table 13 summarizes the results seen with these chemicals. In general, the compounds DES, CY, BP, INDO, and TCDD were highly immunosuppressive affecting cell-mediated immunity and T/cell function, antibody PFC formation and host resistance parameters; OPP and TCPP demonstrated minimal or no immunotoxicity. Lymphoproliferative responses to T-cell dependent mitogens and resistance to tumor, bacterial or parasite challenge represented the most sensitive parameters of immunotoxicity assayed. The proposed mechanisms responsible for the immunotoxicity observed a given in Table 14.

Development continues on bone marrow progenitor and host resistance assays. During the past decade a variety of *in vivo* and *in vitro* assays have been developed to examine the functional state of hemopoietic progenitor cells from the bone marrow. These assays have not only aided in understanding the control and regulation of hematopoiesis but, more importantly, are uses as sensitive clinical indicators for myelotoxicity induced by chemotherapeutic drugs. However, little if any attention has been directed toward their potential as toxic indicators in the examination of chemicals of environmental concern. This appears rather surprising in view of the numerous chemicals that induce hematological alterations including anemia or myelosuppression. To date the NTP immunological toxicology program has examined the effects of several chemical pollutants on hemopoietic progenitor cell assays (Table 13). Preliminary data indicate that these assays may be used as an earlier indicator of cellular and immunotoxicity with most, but not all, chemicals.

FY 1981 Program Plans

Research on methods selection will continue in NTP laboratories during FY 1981 with emphasis on developing correlations between host resistance and immunological parameters. Alterations in host resistance appear from preliminary studies to be sensitive indicatorsa of immunotoxicity. For some time, a correlation has been found between the use of chemical immunosuppressants in clinical medicine and increased incidence of bacterial, viral, fungal, parasitic and neoplastic dieases. Through cooperation with FDA laboratories in Cincinnati, Ohio, and Jefferson, Arkansas, NTP will examine *in vivo* and *in vitro* approaches to immunological evaluation, including the evaluation of interferon production and the application of laser cytometry as an indicator of immunotoxicity and host resistance parameters. Contracts will be awarded during the first quarter of FY 1981 to assist with the development of host resistance models using viruses, bacteria, parasites, and tumor cells. In addition, the immunological panel will be validated using selected chemicals, and will be correlated with the host resistance panel developed in the first phase of the contract. An interlaboratory comparison of selected methods also will be initiated between contract and NTP laboratories during the second quarter FY 1981.

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TABLE 13

SUMMARY OF FY 1980 STUDIES OF VARIOUS CHEMICALS ON IMMUNE AND HOST SUSCEPTIBILITY PARAMETERS[a]

Chemical	RBC Counts	WBC Counts	Thymus Weight	Bone Marrow Progenitor Cell Proliferation	Antibody PFC Response	Serum Antibody Titer	Immunoglobulin Levels	Lymphoproliferative Responses
Diethylstilbestrol (DES)	NE	↓↓	↓↓	↓↓	↓	NE	↓	↓↓
Cyclophosphamide (CY)	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
Orthophenylphenol (OPP)	NE	NE	NE	NE	NE	NE	NE	NE
Tris (1,3,-dichloro-2-propyl) phosphate (TCPP)	NE	NE	NE	NE	NE	NE	NE	↓
Indomethacin (INDO)	ND	ND	NE	↑	↑	ND	ND	↓
Benzo(a)pyrene (BP)	NE	↑	↓	↓↓	↓↓	↓	↓	↓
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (perinatal exposure) (TCDD)	↓	NE	↓↓	↓	ND	ND	ND	↓↓

CONTINUED

TABLE 13 (Cont'd)

Chemical	Delayed Hypersensitivity Responses	Macrophage Functions	Resistance to Syngeneic Tumor Cell Challenge	Resistance to Bacterial Challenge	Expulsion of Parasite	CAS No.
Diethylstilbestrol (DES)	↓	↑↑	↓↓	↓↓	↓↓	56-53-1
Cyclophosphamide (CY)	↓↓	↑	↓↓	↓↓	↓↓	50-18-0
Orthophenylphenol (OPP)	NE	NE	NE	NE	NE	90-43-7
Tris (1,3-dichloro-2-propyl) phosphate (TCPP)	NE	NE	↓	NE	↓	13674-87-8
Indomethacin (INDO)	NE	↑	NE	NE	NE	53-86-1
Benzo(a)pyrene (BP)	NE	NE	NE	NE	↓	50-32-8
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (perinatal exposure) (TCDD)	↓	NE	↓	↓	ND	1746-01-6

[a]Represents general effects following evaluation at 3 chemical dosage levels. Dosage levels examined were below that which induced signs of overt toxicity such as decreased body weight gain. Several chemicals induced slightly altered liver function (e.g., DES and OPP) but their effect was not related to immune dysfunction.

NE = no effect; ND = not done; ↓ = slight to moderate decrease; ↓↓ = marked decrease; ↑ = slight to moderate increase; ↑↑ = marked increase.

TABLE 14

MECHANISMS OF IMMUNOLOGICAL EFFECTS OF CHEMICALS STUDIED IN FY 1980

Chemical	Mechanism of Cellular Toxicity
TCDD	Toxic effects on thymus-dependent lymphocyte through a receptor for TCDD on maturing thymocytes.
DES	Toxic for thymus-dependent lymphocyte function and induces alteration in macrophage function resulting in altered host resistance.
INDO	Affects immunoregulatory circuits.
TCPP	Mild biological alkylating agent with resultant lympholysis.
CY	Potent biological alkylating agent with resultant lympholysis.
BP	Not fully characterized as yet. Primarily affects humoral (B-cell) immunity.

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Neurobehavioral Toxicology

The central nervous system has evolved as a highly specialized organ designed to accept signals from the internal and external environment and to initiate metabolic and behavioral responses of the total organism appropriate to its survival. The complex structure and function of the brain, and the need to simultaneously be protected from the environment and yet be responsive to it, make it uniquely susceptible to environmental insults. It is believed that behavioral and neurologic alterations in response to exposure to environmental pollutants often may represent the earliest manifestations of toxicity in animals. Thus, it is most relevant to the mission of the National Toxicology Program that test systems be developed and chemicals be tested for neurobehavioral effects.

The NTP neurobehavioral program involves the formation of a strategy for the development, standardization and validation of neurobehavioral screening tests. Such a test battery would provide a general indication of the presence of neurotoxicity, and would possibly indicate the type or nature of neurotoxicity in terms of neurobehavioral function that may be affected. Known representative neurotoxicants are studied in the battery to determine the level of sensitivity and selectivity of each component test. This battery with continuing refinements is used as part of the general toxicology screen and in the prechronic phase of the two-year carcinogenesis bioassay.

An additional objective is the development of a test capability for more extensive in-depth toxicological characterization of selected chemicals either identified in preliminary neurobehavioral screening or which are of public health concern.

FY 1980 Accomplishments

The neurobehavioral toxicology program involves laboratories at two NTP agencies. During FY 1980, a document was written which reviewed recommendations for appropriate research strategies in neurobehavioral toxicology which had been made at several recent workshops. The document identified those recommendations relevant to NTP and the extent of their implementation.

The standardization and validation of a test battery for the neurobehavioral assessment of potential neurotoxins continued under contract. This was being accomplished by evaluating the effects of tetraethyl tin, methyl mercury, sodium salicylate, D-amphetamine, acrylamide, arsenic, lead acetate, chlordecone (Kepone), and triethyl lead chloride on male rats of the Fischer 344 strain. Tests being evaluated included measures of sensory and motor functioning and indicators of learning ability.

Studies with Kepone demonstrated that adult rats exposed to 10 or 30 parts per million in the diet for a period of 90 days exhibited neurotoxicity as indicated by behavioral hyper-reactivity. In another study, female rats were fed Kepone in the diet for 60 days prior to mating. Dietary exposure continued throughout gestation and during lactation until the pups were 12 days of age. Male and female pups were being tested for neurobehavioral alternations at 30 and 90 days of age using a battery of tests consisting of startle responsiveness, negative geotaxis, tail flick, fore- and hindlimb grip strenght, and spontaneous motor activity. At approximately 21 and 100 days of age, rats of both sexes will be sacrificed, their brains dissected and assayed to determine Kepone-induced alterations in neurobehavioral or neurochemical functioning following developmental exposure to low amounts of Kepone encountered in the diet of the mother. This information will be useful in subsequent studies designed to study the neurotoxic mechanisms of Kepone. These studies were initiated in response to concerns expressed by the state of Virginia about human neurotoxicity of Kepone. Studies were also initiated on the neurobehavioral effects of 2,4-dichlorophenoxyacetic acid (2,4-D).

The NTP neurobehavioral toxicology program also conducted human and animal laboratory testing and work site studies of selected chemical agents during FY 1980. Included as part of the animal laboratory work were routine electrophysiological and behavioral screening studies after chronic inhalation exposure of animals to methyl bromide, ethylene oxide, and propylene oxide. Behavioral and neurochemical changes were found in offspring of rats exposed during pregnancy to 2-ethoyxyethanol in the reproductive hazards screening program. New methods were developed for the identification of loss of fine motor control in primates and changes in simple home cage behavior in several animal species. Subtle behavioral effects of toluene and methyl ethyl ketone, and their interaction, were surveyed in human laboratory studies. Similar behavioral changes caused by chronic carbon disulfide exposure were studied in humans in a textile factory. Manuscripts published in the scientific literature during FY 1980 reporting on work recently completed dealt with: chronic and acute exposures to methyl n-butyl ketone and methyl n-amyl ketone (rats and monkeys); acute exposure to carbaryl (rats and monkeys); gestational exposure (and testing in offspring) to 2-ethoxyethanol (rats); and acute exposures to methylene chloride and ethanol (human volunteers).

FY 1981 Program Plans

The standardization and validation of a test battery for neurobehavioral assessment of potential neurotoxins will be completed late in FY 1981. Automated procedures to assess toxicity in animals, using simple home cage behaviors such as eating, drinking, and motor activity, will be assessed using large numbers of animals in home cage-like environment. In addition, studies on the neurobehavioral toxicity of chlordecone and 2,4-D will continue.

Another effort will be to screen inhaled ethanol, 2-ethoxyethanol, propylene oxide, ethylene oxide, methyl bromide, tri ortho cresyl phosphate, and lithium compounds for neurotoxicity using neurobehavioral and neurophysiological tests. Interaction effects will be tested using exposure to selected combinations of toluene, methyl ethyl ketone, xylene, acetone, and ethanol in humans; and a job task stressor, forced pace, plus acetone in animals. Methods development work will utilize primates, implementing tests of fine motor control, and rodents, developing screening tests of sensory loss. Paint sprayers will be tested at the work site in order to characterize neurotoxicity in select worker populations having chronic exposures to assorted solvents.

An interlaboratory collaborative study is planned to identify and develop screening methods for measuring effects of prenatal exposure to chemicals on behavior during animal development. This study is described in the section on Reproductive and Developmental Toxicology.

Pulmonary Toxicology

Although many substances are assessed toxicologically by the inhalation route of exposure, pulmonary function testing is often neglected. The lung is often a prime target organ in addition to being a route of entry for systemtic intoxication. In recent years techniques have been developed that measure indices of pulmonary function in rodents—static and dynamic lung volumes, mechanical properties, gaseous diffusion, distribution of inspired air and

more recently, ventilatory performance. Use of these indices may help discover whether examining pulmonary function provides more toxicologic information than does pathologic evaluation of lung injury. Pulmonary function tests in animals must be accurate, precise and specific as well as very sensitive if they are to be used effectively in diagnosis of early and/or subtle pulmonary pathologic changes seen in animal models for chemically-induced pulmonary disease in humans.

FY 1980 Accomplishments

Through an Interagency Agreement, the NTP has initiated studies to evaluate the benefits of using respiratory function techniques in toxicity evaluations of compounds. A study exposing male rats to filtered conditioned air containing 0.2, 0.8, and 2.0 ppm ozone was completed during FY 1980. All animals were exposed for 6 hrs/day, 5 days/week for a duration of 63 exposure days. Experimental data are undergoing statistical analyses. Exposure of male rats to acrolein began later in the year. The experimental regimen was identical to the one employed for ozone; airborne concentrations were 0.4, 1.4 and 4.0 ppm. This study will be completed during FY 1981.

FY 1981 Program Plans

Statistical analyses and evaluation of the findings from the inhalation exposure studies with ozone and acrolein will be completed in FY 1981. Three additional compounds will be evaluated in FY 1981, one of which will have an expanded duration of exposure and a subsequent non-exposure holding period to assess recovery or exacerbation of the response.

Reproductive and Developmental Toxicology

The assessment of chemical agents for effects on reproductive function and developmental toxicity is of critical importance for estimating risk from human exposure. Techniques for evaluating reproductive and developmental toxicology have generally involved standardized whole animal test systems and as such provide only crude indictors of reproductive effects or developmental abnormalities. The underlying biological mechanisms which account for these major health problems are still unclear in part because of the complexity of the developmental and reproductive processes. An increasing number of environmental agents have been demonstrated to have adverse effects on reproduction and development. With the large number of compounds to be tested and the limited resources available, the NTP effort is directed primarily toward the use of conventional testing procedures and improvement of these procedures. Development and validation of new methods which will be more sensitive, specific and reproducible is being pursued at a modest level.

FY 1980 Accomplishments

The testing of chemicals for teratogenic potential in FY 1980 included the evaluation of 21 chemicals. Final reports were received in FY 1980 for these chemicals, and the results are shown in Table 15. In studies of teratogenicity, both maternal and fetal toxicity are assessed. Maternal toxicity is determined by lethality or a reduction in weight gain during pregnancy. Fetal toxicity is indicated by increased prenatal death, reduced fetal weight and/or an increased incidence of malformed fetuses. When fetal toxicity occurs only at dose levels producing maternal toxicity, the fetal effects may be secondary to maternal effects and thus are not considered as serious a finding as when fetal toxicity occurs below maternal toxic doses. In Table 15, positive effects are indicated only in those cases where feto-toxicity occurred at doses below those producing maternal effects.

Chemicals selected for testing by the NTP Executive Committee (see Table 16) are being reviewed and a literature file of toxicity information and any available teratology data is being established. From this information, protocols which are most appropriate for testing each particular chemical will be developed jointly by the contractor and the NTP.

The histopathologic examination of fetuses to detect lesions not obvious with conventional methods was completed in FY 1980. Fetuses from pregnant mice exposed intravenously to ethylene oxide did not reveal any alterations that could not be detected in the routine examination. Studies are currently underway with additional agents.

In the area of reprodution and fertility, studies were undertaken during FY 1980 evaluating the effects of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on male fertility (Table 17). Male mice were treated with mixtures of these chemicals (components of the herbicide "Agent Orange") and the males were bred to untreated females. Fertility (% fertile matings) and sperm quality (% abnormal sperm, and sperm concentration and motility) were evaluated. Also, the offspring underwent teratologic evaluations. No significant decrements infertility or reproduction were found, and there was no evidence of germ cell toxicity. Survival of offspring and neonatal development were apparently unaffected by paternal exposure to the simulated mixtures of "Agent Orange".

Other chemicals already under specific test include dibromochloropropane and chlordecone (Kepone) (Table 17). These chemicals, which are known to alter reproduction in humans, are being used to help validate assay reliability and to increase understanding of their specific mechanisms of toxicity.

Priority chemicals, selected on the basis of usage and the extent of exposure, are being screened to determine potential reproductive hazard through germ cell mutations. Test systems used as *Drosophila* sex-linked recessive lethal (SRL), rat dominant lethan (DL), and mouse sperm head morphology (SHM). Chemicals under test in FY 1980 are listed in Table 17.

In the area of postnatal development, a project on the effect of maternal lead exposure on offspring was initiated in FY 1979 and will be completed in FY 1981. Lead acetate was administered in the diet to maternal rats and the functional status of various organ systems in their offspring was investigated and correlated with maternal blood lead levels. Oxygen metabolism and selected hematopoietic effects have been investigated. The cardiovascular system is presently being examined and the renal system was also under study in FY 1980.

Functional and psychomotor development in rats were studied by NTP in FY 1980 following exposure of pregnant females to 2-ethoxyethanol at 100 ppm. Developmental impairment and neurochemical alternations were observed in the offspring, and embryotoxicity was observed at high concentrations. Potential interactions between ethanol and 2-ethoxyethanol are presently being studied and should be completed in FY 1981.

Behavioral and cognitive disorders are among the more common congenital problems observed in children. A number of chemicals have been shown to produce behavioral dysfunction postnatally in animal studies. Although the need for the behavioral evaluation of neonatal animals in the safety assessment of new drugs and chemicals is evident, standardized, reliable and sensitive procedures have not been available for testing purposes. An interlaboratory collaborative study is planned to identify screening methods which yield valid and reproducible

results within and among laboratories. The methods will be evaluated based on their sensitivity to toxic alterations produced by three known behavioral teratogens which represent a range of chemical classes (Vitamin A, methylmercury and d-amphetamine). The dose-finding study for the intramural pilot segment of the collaborative study is underway and will be completed in FY 1981.

FY 1981 Program Plans

A new contract to continue conventional teratology testing of 10–12 chemicals per year was awarded. The contract also permits single or multigeneration studies and functional testing if needed.

Teratogenesis studies using inhalation exposure of ethyl benzene and 2-ethoxyethanol are scheduled for completion early in FY 1981. Studies by other routes of exposure on diphenhydramine, ethylene chlorohydrin, ethylene oxide (rabbit), phenol, and bisphenol A are due to be completed and reported on in FY 1981. A contract for teratogenesis testing of ethylene oxide, propylene oxide, and n-butyl acetate by inhalation was awarded in the fourth quarter of FY 1980.

In the area of fertility and reproduction, thirteen compounds are being screened under contract in five Tier II mutagenesis tests scheduled for completion in June 1981 (Table 17). The test systems being employed are *Drosophila* sex-linked recessive lethal (SRL), rat bone marrow cytology (BMC), mouse sperm head morphology (SHM), rat dominant lethal (DL), and *in vitro* unscheduled DNA synthesis in human fibroblasts (UDS). The compounds being tested are allyl chloride, bis(2-methoxyethyl)ether, butylene oxide, cyclohexanone, N,N-dimethylacetamide, dimethylformamide, hexachlorobutadiene, 2-methyoxyethanol, methyl bromide, N-methyl dicyclohexylamine, 2-nitropropane, styrene oxide, and 1,1,2,2-tetrachloroethane.

The pilot segment of the interlaboratory study on behavioral teratology will begin following delivery and approval of a microprocessor system early in FY 1981. Contracts or interagency agreements with six cooperating laboratories in the collaborative study will be awarded in FY 1981. Although the protocol for the study has been planned for some time, procedures are continually being refined using information from the pilot study and new information appearing in the literature. Consultation with experts in statistical analysis of behavioral data is also underway to assure that the most appropriate statistical methods are used. The final results of the interlaboratory study will determine whether or not behavioral tests of this type should be required for routine screening of chemical agents.

The reliability of animal studies for predicting hazard to man is being evaluated in a collaborative project with the Canadian government. In this project, the literature is being examined for concordance of data in terms of types of effects and dose levels in human and animal teratogenicity reports. Information from this project which is scheduled for completion in FY 1981 will be presented at the Toxicology Forum in February 1981. This effort, together with another NTP project involving the examination of the does-response characteristics of teratogenic manifestations, in particular, linearity of the relationship, should provide a better basis for low-dose extrapolation of the teratogenic potential of chemicals.

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TABLE 15

Chemicals for Which Teratology Assays Were Completed in FY 1980

Chemical	CAS No.	Species	Route	Fetotoxicity[b] Prenatal Death	Fetotoxicity[b] Reduced Fetal Weight	Increased Malformations[c]	Maternal Toxicity
n-Butyl acrylate	141-32-2	Mouse	Oral	--	--	+(1 gm/kg)	+(1.5 gm/kg)
Butylene oxide	106-88-7	Rat, Rabbit	Inhal	--	--	--	+(250 ppm)[d]
Carbon disulfide	75-15-0	Rat, Rabbit	Inhal	--	--	--	--
Diethylene glycol diacrylate	4074-88-8	Mouse	Oral	--	--	--	+(60 mg/kg)
1,1-Diphenyl-hydrazine HCl	530-47-2	Mouse	Oral	--	+(200 mg/kg)	+(400 mg/kg)	+(600 mg/kg)
Direct black 38	1937-37-7	Mouse	S.C.	+(100 mg/kg)	+(100 mg/kg)	+(100 mg/kg)	+(150 mg/kg)
Direct blue 6	2602-46-2	Mouse	S.C.	--	+(50 mg/kg)	+(75 mg/kg)	+(100 mg/kg)
Direct brown 95	16071-86-6	Mouse	S.C.	--	--	--	+(40 mg/kg)
Ethylene oxide	75-21-8	Mouse	I.V. D4-6	--	--	--	+(150 mg/kg)
			D6-8	--	+(150 mg/kg)	+(150 mg/kg)	--
			D8-10	--	--	--	+(150 mg/kg)
			D10-12	--	--	--	+(150 mg/kg)
Formaldehyde	50-00-0	Mouse	Oral	--	--	--	+(200 mg/kg)
2,2',3,3',5,5'-Hexachlorobiphenyl	35694-04-3	Mouse	Oral	+(128 mg/kg)	--	--	--
Methyl bromide	74-83-9	Rat, Rabbit	Inhal	--	--	--	+(70 ppm)[d]
Pentachloroanisole	1825-21-4	Mouse	Oral	--	--	--	+(100 mg/kg)
Perchloroethylene	127-18-4	Rat, Rabbit	Inhal	--	--	--	--
Styrene oxide	96-09-3	Rat, Rabbit	Inhal	--	--	--	+(100 ppm)[e] (15 ppm)[d]
Toluene-2,5-diamine sulfate	6369-59-1	Mouse	Oral	--	+(32 mg/kg)	--	+(48 mg/kg)
Trichloroethylene	79-01-6	Rat, Rabbit	Inhal	--	--	--	--
Xylene (mixed isomers)	1330-20-7	Mouse	Oral	--	+(2.4 ml/kg)	+(2.4 ml/kg)	+(3.6 ml/kg)
m-Xylene	108-38-3	Mouse	Oral	--	--	--	+(3 ml/kg)
o-Xylene	95-47-6	Mouse	Oral	--	+(0.9 ml/kg)	--	+(22.5 ml/kg)
p-Xylene	106-42-3	Mouse	Oral	--	--	--	+(22.5 ml/kg)

[a] All oral and subcutaneous (S.C.) dosing were done on days 6-15 of gestation. Ethylene oxide (I.V.) dosing was at 4 time periods for 3 consecutive days during gestation as indicated. Inhalation (Inhal) exposure to rats with trichloroethylene, perchloroethylene and carbon disulfide included groups with and without pregestational exposure 7 hours/day, 5 days/week for 3 weeks, and gestational exposure on days 1-19 or 7-19; exposure to rabbits was 7 hours/day, days 1-22 or 8-22 of gestation. Inhalation exposure to rats with butylene oxide, styrene oxide and methyl bromide was for 7 hours/day, 5 days/week for 3 weeks prior to gestation, and days 1-19 of gestation; exposure to rabbits was 7 hours/day on days 1-24 of gestation (for methyl bromide, days 1-15).

[b] Numbers in parentheses are the lowest effective dose/day for the endpoint indicated.

[c] Only 3 chemicals produced malformations which were not seen spontaneously in control animals: 1,1 diphenylhydrazine HCl produced ectrodactyly, micromelia and amelia; Direct Blue 6 produced micrognathia; and trichloroethylene produced external hydrocephaly, a rare defect, in a few rabbit fetuses.

[d] Value given for rabbit.

[e] Value given for rat.

TABLE 16

Chemicals Selected for Teratology and Reproductive Toxicology Assays
FY 1981-1983

Chemical	CAS No.
Benzyl alcohol	100-51-6
Butanone peroxide	1338-23-4
Caffeine	58-08-2
Carbon disulfide	75-15-0
Chlorinated dibenzofurans	CHL DIBENZF
Chlorowax 40	63449-39-8
Chlorowax 500C	63449-39-8
Chlorpromazine Hydrochloride	69-09-0
Cinnamaldehyde	104-55-2
Di(2-ethylhexyl)phthalate	117-81-7
1,2-Epoxybutane	106-88-7
Ethylenediamine	107-15-3
Ethylene glycol	107-21-1
Glycidyl ethers	GLYC ETHERS
Hexamethyl-p-rosaniline	548-62-9
Hydrochlorothiazide	58-93-5
Methylene chloride	75-09-2
Naphthalene	91-20-3
Nitrofurazone	59-87-0
p-Nitrophenol	100-02-7
Oxytetracycline Hydrochloride	2058-46-0
Probenecid	57-66-9
Selenium	7782-49-2
Sulfamethazine	57-68-1
Trimellitic anhydride	552-30-7

TABLE 17

Reproduction and Fertility Assays Reported or in Progress
FY 1980-1981

Chemical	CAS No.	Species or Test System	Route
Reported in FY 1980			
2,4-Dichlorophenoxyacetic acid (2,4-D)	94-75-7	Mouse	Diet
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	Mouse	Diet
2,4,5-Trichlorophenoxyacetic acid	93-76-5	Mouse	Diet
Testing in Progress in FY 1980			
Dibromochloropropane (DBCP)	96-12-8	Rat	Gavage
Kepone (Chlordecone)	143-50-0	Rat	Diet
Acrolein	107-02-8	SRL*	
n-Butyl acetate	123-86-4	SRL	
2-Ethoxyethanol	110-80-5	SRL, DL and SHM	
Ethyl benzene	100-41-4	DL	
Ethylene oxide	75-21-8	SHM	
Propylene oxide	75-56-9	DL, SHM	
Vinyl toluene	25013-15-4	SRL	
Tests to be Completed in FY 1981			
Allyl chloride	107-05-1	SRL,BMC,SHM,DL,UDS	
Bis(2-methoxyethyl)ether	111-96-6	"	
Butylene oxide	106-88-7	"	
Cyclohexanone	108-94-1	"	
N,N-dimethylacetamide	127-19-5	"	
Dimethylformamide	68-12-2	"	
Hexachlorobutadiene	87-68-3	"	
2-Methoxyethanol	109-86-4	"	
Methyl bromide	74-83-9	"	
N-Methyl dicyclohexylamine	7560-83-0	"	
2-Nitropropane	79-46-9	"	
Styrene Oxide	96-09-3	"	
1,1,2,2-Tetrachloroethane	79-34-5	"	

*SRL-Drosophila sex-linked recessive lethal; DL-rat dominant lethal; SHM-mouse sperm head morphology; BMC-rat bone marrow cytology; UDS-in vitro unscheduled DNA synthesis in human fibroblasts.

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Coordinative Management Activities

Chemical Nomination and Chemical Selection

More chemicals are nominated for NTP consideration than can be selected for study. Early recognition of this problem led the NTP Executive Committee to formulate a set of selection principles (Table 18). These eight chemical selection criteria motivate a matrix which operates throughout the NTP (Figure 3).

Most chemicals are nominated and selected for testing because toxicologic information is lacking and because the potential exists for human exposure. Other important criteria include production levels, physical and chemical properties, interest by government agencies, and possible significance for public health. The toxicology testing strategy is to identify the major toxic effects for each chemical studied. In addition to identifying chemical mutagens and carcinogens, this includes causation of damage to critical target organs such as the lungs, liver, and nervous system. Thus, Phase I tests (see Table 2) result in a core of toxicology data essential to the proper design of more extensive studies. As an example, using the information from the Phase I rodent toxicologic screen, Phases II and III testing can be started with increased capabilities to confirm and better define toxicities identified in the screen.

The NTP urges those interested in proposing a chemical or chemicals for testing consideration to explain the rationale for the nomination, to recommend the type of tests to be considered, and to supplement each nomination with as much of the necessary information as possible (see Table 19). All nominations are considered regardless of the depth of the information submitted. Nominations should be addressed to Chemical Nominations, National Toxicology Program, Room 3A–10, Landow Building, National Institutes of Health, Bethesda, Maryland 20205.

To encourage nominations, an announcement seeking chemical nominations was made in the February 8, 1980 **Federal Register**, and 973 request letters were sent to (1) consumer groups, (2) labor unions and labor safety officials, (3) occupational newsletters and publications, and (4) trade and professional associations. Furthermore, a call for nominations appeared in the April 1980 issue of the *NTP Technical Bulletin* mailed to 2,915 scientists and administrators actively engaged in toxicology and associated research. The chemical nomination procedure was explained and requests made for nominations at interagency and public meetings held in June 1980.

All nominations received are first screened to see if the chemical has already been tested, is under test, or is scheduled for test. If the chemical fits into any of these classes, this is made known to the nominator. Nominations outside these categories are forwarded to the NTP Chemical Review Group. The group examines the accompanying information, uses the current and appropriate literature sources, prepares executive summaries of relevant information, and submits these chemical overviews to the NTP Chemical Evaluation Group. This group includes representation of the agencies on the NTP Executive Committee: CPSC, EPA, FDA, NCI, NIEHS, NIH, NIOSH, and OSHA. The Evaluation Group proposes priority and testing needs to the NTP Executive Committee. The Executive Committee considers these recommendations together with the executive summaries and decides to approve a chemical for testing, defer it for more information, or disapprove the nominated chemical. Executive Committee decisions are published in the *NTP Technical Bulletin*. The Executive Committee also recommends priorities for testing and test development/validation to the NTP.

The selection of a chemical by the Executive Committee does not automatically commit the NTP to testing the chemical. The NTP is committed to ascertain the specific toxicologic and regulatory concerns; evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and then propose and conduct specific tests that are needed. Occasionally new information is obtained that answers the questions posed in the nomination and selection process. Sometimes testing is not done because chemicals are withdrawn by the nominator, because others are or will be testing the chemical, or because the chemical is not available, or no longer produced.

The NTP Board of Scientific Counselors Chemical Nomination and Selection Subcommittee reviewed the procedures by which chemicals are nominated and selected for testing, surveyed the methods used for proposing specific testing requirements, and identified those areas needing further development. A major objective of the Subcommittee is to ensure public input into the chemical nomination and chemical selection process. Recommendations should be forthcoming from this Subcommittee during the first quarter of FY 1981.

For FY 1980, 126 Executive Summaries were prepared. Also, ten mini-monographs have been prepared in draft form and should be ready for distribution in the first quarter of FY 1981: butyl nitrite, capsaicin, cinnamaldehyde, 1,4-cineole, 1,8-cineole, ethyl benzene, glutaraldehyde, rotenone, sulfamethazine, and trimellitic anhydride. Approximately four hundred compounds have been listed and submitted for potential mutagenicity testing. More nominations for mutagenicity consideration will be submitted in the first quarter of FY 1981.

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TABLE 18

NTP CHEMICAL SELECTION PRINCIPLES

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. Therefore, the NTP, acting under its chemical selection principles, will test:

1. Chemicals found in the environment that are not closely associated with commercial activities;

2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement;

3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry;

4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal government is justified to verify the results;

5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods;

6. "Old chemicals" with the potential for significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws);

7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved); and

8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing.

FIGURE 3

NTP CHEMICAL NOMINATION AND CHEMICAL SELECTION PROCESS

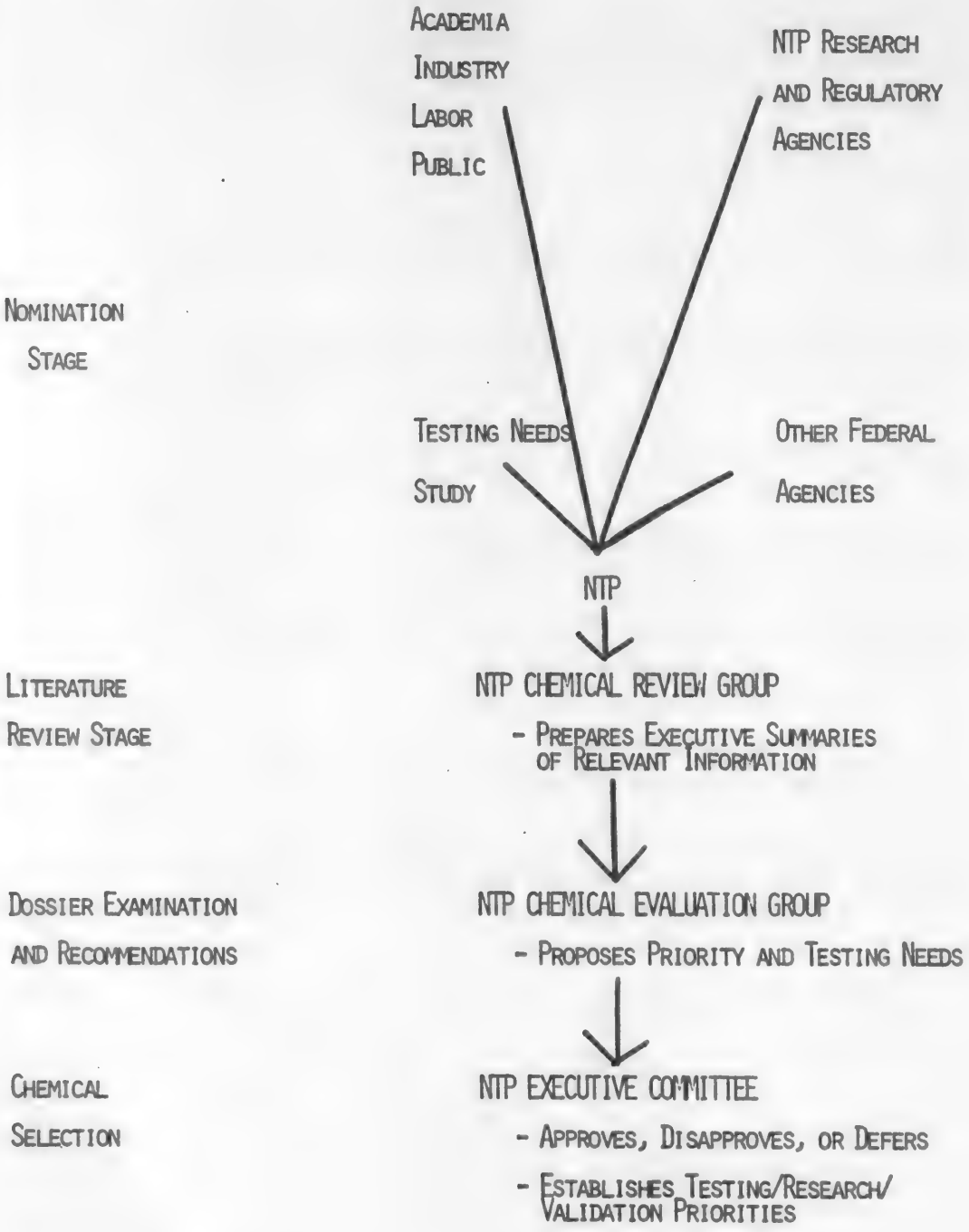

TABLE 19

NTP Chemical Nomination Elements

I. Chemical Identification

- a. Chemical Abstracts Service (CAS) preferred name
- b. Common or generic name and synonyms
- c. CAS Registry Number
- d. Chemical class and related compounds
- e. Physical and chemical properties
  - i. Physical description
  - ii. Structural and molecular formula and molecular weight
  - iii. Melting and boiling points
  - iv. Solubility
  - v. Stability and reactivity
  - vi. Other relevant information
- f. Commercial product(s) composition
- g. References

II. Production, Use, Occurrence, and Analysis

- a. Production
  - i. Source and synthesis, year and pathway of first production
  - ii. Current production and pathway
- b. Uses
- c. Occurrence in the Environment
  - i. Naturally occurring
  - ii. Air, water, and soil
  - iii. Occupational
- d. Analysis
- e. References

III. Toxicology

- a. Human data, case reports, and epidemiological studies
- b. Experimental animal information
- c. In vitro and other short-term tests
- d. Other relevant information
- e. References

IV. Disposition and structure-activity-relations.

- a. Absorption, distribution, metabolism, and excretion
- b. Structure-activity correlations and considerations
- c. References

V. Ongoing toxicological and environmental studies in the government, industry, and academia

VI. Rationale for Recommendation and Suggested Studies

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Chemical Management

To ensure that each chemical selected for extensive testing is thoroughly evaluated, NTP assigns a Chemical Manager to each compound. It is the Chemical Manager's responsibility to (1) know and understand the relevant scientific literature, (2) present draft protocol designs to the Experimental Design Groups, (3) keep current with the experiment's progress through the Laboratory Monitor, (4) maintain current awareness with the literature, (5) provide liaison with groups doing special tests, (6) assist in data evaluation, (7) draft the reports, and (8) fulfill requests for information on that chemical from interested parties.

The Bioassay Program contracts with commercial laboratories to perform the prechronic and two-year studies. Prior to FY 1980 the monitoring activities were performed by a prime contractor. Starting in FY 1980, the NTP has assigned a Laboratory Monitor to each testing laboratory to be responsible for monitoring the overall operations of the laboratory. The Laboratory Monitor ensures that good laboratory practices are being followed by (1) annual program reviews by peer groups of scientists, (2) quarterly site visits, (3) ad hoc visits by specific disciplines as needed, and (4) constant communication with the laboratory and principal investigator through periodic reports and telephone calls.

Chemical and Pathology Repositories

The chemistry program provides a centralized management system for test and control chemicals. Maintained to assure chemical quality and to minimize testing results variability due to external sources, the chemistry needs are facilitated via integrated contract mechanisms and cooperation and interaction with other NTP operations. The chemistry capabilites provide for procurement, repository functions, chemical analysis, analytical methods development, purification, synthesis, and preparation of chemical safety data handling sheets for approximately 3,000 chemicals.

Capabilities are provided for analyses of bulk chemicals, chemicals in test vehicles, methods development for quality assurance, including purity, stability and concentration determinations, chemical residue analysis for tissues and fluids, and special handling for residual and reprocured chemicals. In addition, capabilities exist for purification, derivatization, and synthesis of test chemicals. Trace level analysis of test chemicals and potential contaminants are available, when required, as well as provisions for percent level purity, stability and recovery analyses. Trace level chemical analyses may be necessary when toxicity tests of chemical mixtures or impure chemicals are positive and it is necessary to identify specific components that may be associated with the observed toxic effect.

FY 1980 Accomplishments

The chemistry program provides primary repository assistance to the mutagenesis and carcinogenesis testing programs. Two repositories have been established which operate under similar standard operating procedures; numerous joint projects have been undertaken that demonstrate integration of the two programs. The remaining chemistry requirements for the NTP toxicity testing programs are supported by another contract for analytical services support.

Throughout FY 1980 several hundred test and control chemicals were provided to investigators. Appropriate quantities for testing newly selected chemicals, in required purity, were procured. In addition, those chemicals selected for testing in the bioassay program were chemically analyzed to ensure they were the correct substances required. The genetic toxicology chemical repository holdings and activities are summarized in Table 20. The carcinogenesis bioassay chemical repository holdings and activities are summarized in Table 21.

FY 1981 Program Plans

Future plans include an extensive update of the repositories' computerized functions, necessitated by the repositories' expanded role in providing the chemistry needs of the various testing programs and for responding to appropriate national and international requests for test chemical samples. In addition, the analytical services support contract will be used to support teratology studies currently being conducted by the Program both in-house and on contract. During FY 1980, 49 chemicals for carcinogenesis bioassay, and 10 chemicals for teratology studies were analyzed. Special analyses were conducted of eight chemical/vehicle mixtures.

Several chemistry contracts and contract modifications in varying stages of completion should meet the increased chemistry needs, particularly in the areas of chemical location, procurement, analysis, synthesis, computer requirements and information retrieval, and preparation of data sheets for safe handling of hazardous chemicals.

Pathology Repository and Archives

The NTP maintains a centralized repository of histopathology materials collected during the bioassay studies. This is done in accordance with Good Laboratory Practice procedures and to provide a complete history of the pathology findings. Storage facilities are provided for wet tissues, paraffin blocks, microscopic slides and printouts of the data that appears in the Technical Reports. User facilities complete with microscopes are provided for investigators to view the materials. For more information or scheduling of user facilities, contact should be made with the Chief, Chemical Pathology Program, NTP, Room 1704, P.O. Box 12233, Research Triangle Park, N.C. 27709; or 919–541–3440 (commercial), 629–3440 (FTS).

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TABLE 20

GENETIC TOXICOLOGY CHEMICAL REPOSITORY HOLDINGS AND ACTIVITIES IN FY 1980

Control chemicals in inventory	24
Test chemicals in inventory	307
Test chemicals sent for Salmonella screen in FY 1980	303
Chemical aliquots sent to date	523*
Chemicals on order/back order	193
Chemicals in preparation/synthesis	3
Chemicals being analyzed	13
Chemical analyses completed	21
Chemicals selected for FY 1980 genetic toxicology testing	320
Chemicals selected for FY 1980 from NCI lists	228

*Includes chemicals other than for Salmonella testing

TABLE 21

CARCINOGENESIS BIOASSAY CHEMICAL REPOSITORY HOLDINGS AND ACTIVITIES IN FY 1980

Chemicals in archive allotment	238
Chemicals in in vitro allotment	295
Chemicals in public distribution allotment	91
Aliquots transferred to genetic toxicology repository	90
Aliquots sent for NCI/NTP genetic toxicology studies	102
Aliquots sent to other investigators	51

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Data Management and Analysis

NTP generates a considerable volume of data from the testing and test development initiatives that must be accurately acquired, stored, and made available promptly for retrieval at multiple locations. For example, in the pathology area approximately two million tissues are examined annually. Thus, a continuing high priority commitment is to develop appropriate automatic data processing (ADP) systems to capture various types of management and experimental data, and to make this information readily available for periodic examination, updating, summarization, and statistical analysis.

In the area of biostatistics new statistical methodologies are being developed for mutagenicity, carcinogenicity, and toxicologic data analysis. Another area of continuing statistical research is experimental design. Modifications in the design of the basic carcinogenesis bioassay are being studied. These may provide a better balance between the high power of detection associated with high dose studies and the low dose information needed for extrapolation methods.

FY 1980 Accomplishments

A review of the ADP requirements of animal bioassay activities was initiated in FY 1980. Following interviews with investigators, the requirements were summarized and the technical criteria that must be met by an ADP system were outlined. This review formed the basis of an ongoing evaluation of the present and future capabilities of the Toxicology Data Management System (TDMS) to meet the ADP needs of the NTP's animal bioassay programs. This system is being developed under an interagency agreement between the carcinogenesis testing program and one of the component agencies of the NTP. The system was designed to provide the following support:

a. Documentation of each nominated compound and tracking of events related to the compound during the review cycle.

b. Analysis of each new experiment and projection of resources requirements for conducting the bioassay.

c. Allocation of animals to the experiment.

d. Collection of weights, clinical observations, and other animal-related data during the conduct of the experiment.

e. Collection of pathology results.

f. Maintenance of complete experiment status summary for all bioassays.

g. Generation of a draft report for each bioassay which will aid in the development of the published final report.

TDMS is now undergoing evaluation, using both manual and automated techniques, at a contract laboratory doing carcinogenesis bioassays and by NTP personnel. Final testing of the software for source data collection as well as for stand-alone administrative functions at the bioassay contractor laboratories is dependent on procurement of the microprocessor-based intelligent data collection terminals scheduled for delivery early in FY 1981.

As part of the review process three ADP consultants assisted in the evaluation of TDMS and are identifying modifications that might enhance its capability to support the bioassay program more effectively. This review has been completed and the report will be submitted during the first quarter of FY 1981.

In other ADP studies, efforts have been made to provide a computerized system to allow storage and retrieval of management information about research activities. Several data base and file management systems have been evaluated for potential usefulness. An interim chemical tracking system has been implemented on an in-house minicomputer, and a replacement system is under development using a System 204.

The mutagenesis testing program is being supported by a computerized data base management system which allows timely and accurate collection and retrieval of laboratory test data. The system summarizes results, produces reports, and provides analyses to support mutagenicity determinations. The system is being developed further using the PROPHET system.

In FY 1980 ADP data systems support for the carcinogenesis bioassay program was provided by the Carcinogenesis Bioassay Data System (CBDS), some limited administrative management support systems, and other reporting systems. The CBDS facilitates the collection and reporting of information on chemical and animal data, clinical observations, and individual animal pathology. CBDS also contains chemical and Standard Nomenclature on Pathology (SNOP) code dictionary files. Reports from CBDS are used extensively by the bioassay program, particularly in the pathology, statistical analysis, and technical information areas.

Additional systems development includes (1) a Strain A Mouse system, which collects and reports information to assist in the administration of the Strain A studies, the evaluation of the results, and the comparison of the data with other *in vivo* and *in vitro* studies; and (2) a management and resource tracking system, which provides various monthly and quarterly management reports for the animal bioassay program.

Biostatistics research conducted to date on the microbial mutagenicity experiments indicates that a negative binomial sampling distribution for *Salmonella* test plate counts represents a significant improvement over the widely adopted Poisson model. A family of models has been constructed to relate the average plate count to the chemical dose administered per plate. Those models include genetic and cellular toxicity as competing risks, *vis a vis* mutation for all microbes. The "single-hit" model for radiation mutagenesis experiments is a special case of the group models.

For other toxicological data the use of randomization procedures for the analysis of binary response data is being investigated. The power of these procedures is being compared with that of alternative nonparametric techniques. During FY 1980 a Monte Carlo study was done on the power of some k-sample tests for ordered binomial alternatives. For small group sizes "exact tests" were found to be based on isotonic regression and Armitage's test for linear trend and similar power. However, "exact tests" appear to be less sensitive to reverse alternatives and more powerful for larger group sizes than the Armitage procedure.

In FY 1980 research continued on the statistical aspects of chronic carcinogenesis testing: competing risk techniques, cause of death assumptions, time-to-tumor model and simultaneous inference on multiple sites and types of tumors. During the past year an investigation began on the possible modifications of the basic bioassay design with regard to (1) choice of doses, (2) number of dose groups, and (3) number of animals per group. The major objective was to determine if the low dose extrapolation potential of the bioassay could be improved without seriously sacrificing the ability to identify carcinogenic chemicals.

The degree to which low dose extrapolation is altered by replacing the administered dose with the amount of DNA-carcinogen adduct formed was evaluated and found to be highly model dependent. Efforts are now being made to identify those pharmacokinetic

parameters which exert the most influence on the low dose risk estimate.

FY 1981 Program Plans

Based on the review of data systems by the ADP consultants, NTP will develop an action plan to enhance the TDMS capability to support most effectively the program needs. TDMS will begin to be installed in the second quarter of FY 1981 at a contract laboratory. This phase, to correspond with the initiation of a new two-year bioassay study, will provide an in-depth evaluation of all major modules of TDMS under actual conditions. Based on performance, necessary modifications and refinements will be made and integrated into the evaluation process.

In management information systems, FY 1981 activities will include continued development of the System 204. Currently the interim system is operational and awaiting modification and expansion by staff.

During FY 1981, work on the computerized data base system for the mutagenesis testing program will include further refinement of system capabilities as well as increased collection of data. The current level of ADP systems support for the carcinogenesis bioassay program will be maintained in FY 1981.

Development of appropriate technologies to process the large volume of data that will be generated from the various animal studies will continue. In FY 1981 various alternatives will be explored (e.g., a contract with a data processing organization) and a decision will be made as to how data summarization, statistical analysis, and report generation might be best effectuated. The long-term solution to this problem will involve the implementation of a comprehensive ADP system, such as TDMS, to handle many of these activites.

For biostatistics in FY 81, there will be a continuation of ongoing efforts in development of new statistical methodology, particularly for the prechronic toxicology studies and certain other special studies (e.g., metabolism, clinical chemistry, behavioral toxicology) that will begin to generate data during FY 1981.

The new family of models constructed to relate the average plate count from *Salmonella* test protocols to the test compound dose administered per plate will be fit to a file of over 600 *Salmonella* tests performed on contract. The need for further model refinements will be studied, as well as such issues as assay reproducibility within a laboratory or between laboratories.

A study to determine if the low dose extrapolation potential of the carcinogenesis bioassay could be improved will continue in FY 1981.

Laboratory Animal and Quality Control

The laboratory animal program provides quality animals for the bioassay program, monitors these animals for disease before they enter the bioassay laboratories and assures that the animals are maintained behind barriers and kept free of disease for the duration of the assay.

FY 1980 Accomplishments

Four laboratories are under contract to provide B6C3F1 mice and F344 rats for the NTP bioassay program. Keeping several labs in production will assure a continuous supply of laboratory animals for the bioassay program even when one or more labs may have to stop production due to a disease outbreak. This occurred at one provider laboratory in FY 1980.

The second aspect of disease monitoring is being met by two diagnostic laboratories, one under contract to NTP and one under contract to NCI. Maintaining two diagnostic labs allows cross checks for quality control as well as divides the work load during periods of peak demand.

FY 1981 Program Plans

During the coming year the bioassay animal care program will be more fully described for the participating laboratories. In addition, a policy for the use of detergents and disinfectants in the animal rooms will be formulated. Currently much of the bioassay program monitoring is under the prime contractor. During the next four years this function will be assumed entirely by NTP personnel. This will require a close liaison with personnel from the prime contractor.

Laboratory Health and Safety

Because a majority of the NTP's research and testing involves potentially hazardous materials, laboratory studies must be conducted so as to reduce to a minimum the possibility of human exposure to, or environmental release of, the test materials.

FY 1980 Accomplishments

In addition to health and safety programs at each laboratory participating in the toxicologic testing program (including routine site visits and reviews), efforts are being made to quantitatively define the potential for contamination within a facility resulting from specific testing activities. A work area monitoring program has been initiated to address potential laboratory contamination problems as a function of route of exposure (e.g., dose feed vs. gavage), engineering controls (e.g., animal barrier configurations, different exhaust ventilation designs), work practices, and personnel protection requirements. Results from surveys at several laboratories have indicated potential problem areas that are being addressed on a Program-wide basis.

The NTP recognizes the need for all laboratories participating in the Program to operate in compliance with all appropriate environmental protection statutes relating to the discharge of potentially hazardous wastes. Expanding upon earlier laboratory waste discharge studies, a program was initiated to define the levels of contamination in various waste streams (e.g., cage litter, cage washing wastewater), and to assess the feasibility of incinerating each on site. Further work in waste handling (solid, liquid, and gaseous streams) is necessary to assure compliance with recent hazardous waste statutes.

Several improvements to the administration of the carcinogenesis bioassay program, from a health and safety perspective, have been instituted, including the repacking into smaller containers of those bioassay chemicals received in bulk. Such a procedure serves several purposes: (a) Protective packaging of the material for shipment to the appropriate laboratory is facilitated; (b) Bulk storage at the laboratory is much easier; (c) The repackaging operation can be conducted under much more stringent personnel protection measures than can be achieved by each of the testing laboratories; and (d) The purity of the compound is easier to maintain.

In order to provide additional health and safety support to the testing program, several mechanisms have been developed to provide industrial hygiene/biomedical health and safety services for the program. These efforts include analytical support (e.g., compound-specific permeation studies for protective clothing) as well as support to provide expanded quantitative work area monitoring studies and industrial hygiene assessments of various laboratory activities.

Recently the carcinogenesis bioassay program/NTP sponsored a conference on the alternatives in the design and operation of toxicologic testing facilities which provided a forum for the discussion of several contrasting viewpoints regarding laboratory animal care and personnel health and safety.

FY 1981 Program Plans

Several areas will receive emphasis in FY 1981, including the disposal of potentially contaminated wastes associated with toxicologic testing activities, expansion of existing medical surveillance procedures to include indices of exposure of biological response in individuals working with biotest materials, cooperative efforts to evaluate methods of *in situ* decontamination of personnel and lab equipment that may have been inadvertently contaminated with test materials, and an expanded effort to quantitatively define the risk of personnel exposure to biotest materials during toxicologic testing activities.

Information Generation and Dissemination

The end product of the NTP is information—scientific information about toxic chemicals necessary in deciding societal issues relative to our health and environment. Therefore, communication remains a critical aspect of program success. First, information must be disseminated to other scientists so that peer review assures scientific quality. Second, information must be disseminated not only to the regulators responsible for protecting the public against unnecessary risks, but also to those exposed to the risks. Thus, the NTP has established a coordinated communications network to collect and disseminate toxicologic information.

The value of information produced by NTP depends in part upon the quality and timeliness of information the program receives. The NTP therefore actively seeks information from many sources: Federal, state and local governments; trade associations; industry; labor; academia; professional societies and public interest groups; the press; individuals; other countries; and other interested parties. This includes nominations of chemicals to be tested; critiques and questions about scientific procedures, policies, priorities, and resource allocations; and suggestions for program improvement.

—Scientific Coordination and Information Dissemination

To encourage public participation in the Program, the NTP holds an annual public meeting to introduce the current year's program plans and to solicit comments and advice. The third NTP Open Meeting will take place March 1, 1981, immediately preceding the Society of Toxicology Annual Meeting to be held in San Diego, California. Additionally, the NTP Board of Scientific Counselors convenes three to four times a year in open forum, as does the Board's Technical Reports Review Subcommittee and its *ad hoc* Panel of Experts to conduct peer review on technical reports of carcinogenesis bioassays.

NTP must be aware of scientific procedures and results produced by other laboratories. Part II of the Annual Plan, the *Review of Current DHHS Research Related to Toxicology*, is a major contribution for this effort. Active efforts to learn about work in progress and to establish better communication links among investigators worldwide are being pursued with various national and international organizations.

Fundamental to current awareness is the provision to scientists and administrators of comprehensive searches and/or reviews of the world's scientific and technical literature on a given compound, in advance of decisions about priorities and experimental test designs. This is of special importance for the carcinogenesis bioassay program, where each test represents a major commitment of time, labor, materials and funds for up to a five-year period.

Toxicologic research and testing require a high degree of scientific coordination for information generation and dissemination. To better utilize the tools of information science, the NTP has a cooperative agreement with the National Library of Medicine (NLM). The on-line services available from the NLM are particularly valuable: CHEMLINE, TOXLINE, RESEARCH PROJECTS, MEDLINE, CANCERLINE, TOXICOLOGY DATA BANK, RTECS (Registry of Toxic Effects of Chemical Substances), and others. These and other sources are used to prepare dossiers on chemicals nominated for test and to design test protocols. Also, new information services will need to be located or developed as needed for toxicology specialties not yet covered adequately in existing systems—for example, neurotoxicology, chemical immunotoxicology, and chemical-chemical interactions.

The Environmental Mutagen Information Center (EMIC), supported by the NTP, collects, organizes, and disseminates primarily published information on chemicals tested for mutagenicity. Located since inception in 1969 at the Oak Ridge National Laboratory (ORNL), the EMIC computerized data file contains 33,396 records on 9143 unique chemicals, 28,039 of which are available online from TOXLINE (at the National Library of Medicine) and from RECON (at the ORNL). Each record contains bibliographic information, assay systems, and keywords defining agents tested and organisms studied.

The Environmental Teratology Information Center (ETIC), at ORNL, also supported by the NTP maintains a computerized collection of published information on chemicals tested for or known to induce teratogenic effects. The file contains reference to 20,413 literature citations; 18,299 records are available from TOXLINE and RECON.

The NTP, and in particular the Technical Information Section, supplies information to Congress, scientists, the public, regulatory agencies consumer advocates, labor, legal organizations, industry, and others. During FY 1980, for instance, the NTP responded to 2,500 requests for technical information.

—Technical Report Preparation and Dissemination

The major responsibility of the Technical Information Section, however, is to provide the carcinogenesis bioassay program's chemical managers with the most relevant information necessary to oversee the progress of a compound from selection through carcinogenesis testing to final report preparation and distribution. Preparation of the technical report begins with selection of a chemical for testing and appointment of a chemical manager. Each manager is responsible for records management throughout the test and preparation of the draft carcinogenesis bioassay report. While experiments are in progress, the chemical manager interacts with other Government agencies and serves as resource person for scientific inquiries concerning the chemical and its possible adverse effects. Lists of chemicals scheduled for testing, those on test, and those already completed will be published routinely in the **Federal Register**, the Annual Plan and the NTP Technical Bulletin as well as being distributed to a variety of newsletters and scientific magazines.

Further, NTP uses various toxicologic information resources for extensive literature searching and acquisition of scientific papers. Included are a number of information organizations in the private sector which extend the capability of the NTP, and these organizations are available on short notice through interagency or basic ordering agreements. In FY 1980, 81 comprehensive literature searches were performed for the chemical manager by the Toxicology Information Response Center (TIRC). From these, the most important references were selected for inclusion in an experimental design package sent to reviewers for generating

the protocols for carcinogenesis bioassay testing.

—Tracking of Chemicals and Test Statuses

The Technical Information Section also updates the computerized management status file for chemicals in various stages of carcinogenicity testing, producing a computerized listing on all chemicals. These lists are distributed quarterly on an individual basis to those who have a need to know about the movement of chemicals through the program.

For administrative purposes a unique numbering system for select chemicals was devised and NTP numbers, corresponding CAS Registry Numbers, and references to tables in the Annual Plans in which each chemical appeared were computerized.

Further, a prototype NTP Chemical Registry Handbook was prepared which contains for each compound the generic name and NTP number, the CAS name and Registry Number, molecular formula, and references to online services containing more information about the compound. Indexes by CAS Registry Numbers, molecular formulas and names are included. In early 1981, the Handbook will be distributed to NTP scientists and administrators as well as being offered to anyone upon request.

A Literature Search Tracking System was designed to monitor the status of literature search requests. This system, based on individual compounds records, is being expanded considerably to function as an interm online chemical tracking system.

—International Coordination

In partnership with the international community, the NTP is striving to formulate a universally-based communication network of toxicologic information. Concomitantly, the NTP is seeking active participation from toxicologists throughout the world. The NTP will continue to explore and develop liaison with foreign agency counterparts. For instance, contacts have been established with the World Health Organization's International Program on Chemical Safety, with the International Agency for Research on Cancer, with the International Registry of Potentially Toxic Chemicals, and others.

—Public Awareness and Inquiry Responses

The newly established NTP Public Information Office is responsible for assuring that general information about the Program is disseminated widely among the scientific and public media: results of NTP problem-oriented research such as studies on the herbicide Agent Orange, synthetic fuels development, and hazardous waste dump sites; as well as results of the carcinogenesis bioassay program, the Annual Report on Carcinogens (see p. 113), and other NTP activities. The Public Information Office also answers inquiries from the press and the public about aspects of the Program.

The Public Information Office will publish periodically leaflets and booklets explaining to the public the NTP and its activities, answering questions about environmental health, addressing the benefit-risk question, and explaining basic principles of toxicologic research.

The Annual Plans will continue as the primary reference source for the NTP's research and testing efforts, resources and future plans. The NTP Technical Bulletin serves as the communication medium to those interested in NTP's current and future activities. The Bulletin informs the scientific community, regulators, and the general public on current chemical nomination and selection, test protocols, and research results. Also included are the activities of NTP personnel, the role of the various member agencies, and chemical profiles. Three issues of the NTP Technical Bulletin have been prepared and disseminated: November 1979, April 1980, and November 1980.

In FY 1981, the NTP will attempt to increase awareness of Program activities and capabilities at the level of state government by disseminating the Annual Plan and the Technical Bulletin to the state health departments. Some awareness already exists in that requests for information and nominations of chemicals for testing have been received from such agencies.

To disseminate information, the NTP maintains a computerized inventory of those with an ongoing interest in the Program's activities. The file is divided into broad categories: labor, industry, government, lawyers, researchers, consultants, academicians, public interest groups, scientific and national media, and other individuals who have expressed an interest in keeping aware of current activities. This growing file includes 2,915 names and addresses. Names are added to the registry on request.

Annual Report on Carcinogens

In July 1980, the First NTP Annual Report on Carcinogens was published and distributed. The report was prepared pursuant to a 1978 amendment, Section 301(b)(4), of the Public Health Services Act which requires the Secretary, DHHS, to publish annually a list of "all substances which are either known to be carcinogens or which may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed * * *." Each Annual Report must also contain information on the nature and degree of exposures to such carcinogens and on the extent to which Federal regulations are effective in reducing the risk to public health.

The First Annual Report focuses on 26 chemicals and industrial processes which the International Agency for Research on Cancer (IARC) evaluated with respect to induction of cancer in humans. For each of the 26, the Report summarizes available estimates of how many people are exposed both at home and in the workplace, and summarizes the available evidence of carcinogenicity as demonstrated by human and animal studies. For each of the chemicals and industrial processes, tables provide information on: domestic production and imports; how the product or process is used; the numbers of people exposed; as well as the route, frequency, and level of exposure; and the applicable Federal regulations. Data selected from the IARC Monographs and the original submissions from the Federal agencies are also included.

Although Federal agencies have been collecting information on—and regulating—carcinogens for years, this is the first time that this information has been assembled in a single report. The Annual Report thus represents an important medium for informing the public and policymakers on the status of substances considered likely to be carcinogenic for humans. Even though science and society have not arrived at a final consensus on the definition of a carcinogen, either in the human population or in experimental animals, prudent public policy dictates that regulation of possibly hazardous substances should not wait until there is human evidence of cancer. It is therefore important that evidence from studies on experimental animals be used as a basis for regulation to prevent exposures.

The report notes that over the past two years significant progress has been made in developing a consensus that, for the purposes of regulation, positive, well-conducted studies on laboratory animals provide presumptive evidence of the potential for human carcinogenicity.

Because the First NTP Annual Report on Carcinogens represents NTP's initial effort to identify carcinogens and document the available evidence, to estimate human exposures, and give the current status of public health

regulations, by necessity it focuses on those 26 chemicals and industrial processes which IARC—an agency of the World Health Organization—found in evaluating the scientific literature from 1971 to 1977, to be associated or suspected to be associated with human cancer.

The Report cautions that there are more than 26 known human carcinogens; just because a substance is not listed in the First Annual Report does not mean that it is not a carcinogen.

Future Annual Reports will be expanded to include data on the latest IARC evaluations of chemicals, as well as on chemicals already being regulated as carcinogens but not included in the first Report. The next Report, scheduled for publication in FY 1981, will include information on up to 100 additional carcinogens.

The First Report includes information on three IARC categories of chemicals or industrial processes. Category 1 includes those considered to be "carcinogenic for humans": 4-aminobiphenyl; arsenic and arsenic compounds; asbestos; benzene; benzidine; N,N-bis (2-chloroethyl)-2-naphthylamine; bis (chloromethyl) ether; chloromethyl methyl ether; chromium; diethylstilbestrol; melphalan; mustard gas; 2-naphthylamine; nickel and nickel compounds; soots, tars and oils; and vinyl chloride.

Category 2 includes chemicals or processes that are "probably carcinogenic for humans": aflatoxins; auramine; cadmium and cadmium compounds; cyclophosphamide; and oxymetholone.

Category 3 includes those chemicals or processes which "cannot be classified as to carcinogenicity for humans": chloramphenicol; hematite and iron oxide; isopropyl oils; phenacetin; phenytoin and phenytoin sodium.

The information in the first Report was prepared with the assistance of four regulatory agencies—the Consumer Product Safety Commission; the Environmental Protection Agency; the Food and Drug Administration; and the Occupational Safety and Health Administration—and three research agencies—the Centers for Disease Control/National Institute for Occupational Safety and Health; the National Cancer Institute; and the National Institute of Environmental Health Sciences.

Indexes

The following indexes are provided for this Annual Plan:

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117	Alphabetic Index to Chemicals in Text.
118–125	Alphabetic Index to Chemicals in Tables.
126–130	CAS Registry Number Index to Tables.
131–135	NTP Number Index to Tables.

The Alphabetic Index to chemicals in Tables is organized by a standard IBM sort, which places names beginning with numbers after the alphabet. Thus "nitrobenzene" and "2-nitropropane" are widely separated in this index. The prefixes "D", "L", "O", "M", and "P" are considered as part of the chemical name; thus, "O-nitrotoluene" is sorted under "O", not "N".

Any errors found by the user of these indexes or in the body of the Annual Plan should be called to the attention of: Dr. Larry Hart, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 22709.

Note.—The page numbers in the indexes correspond with the original printed version of the plan.

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